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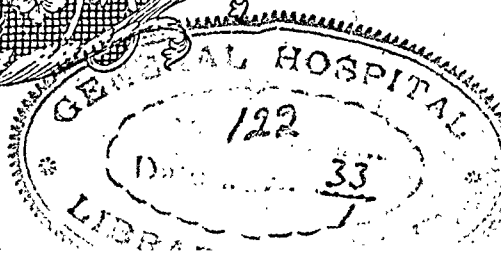
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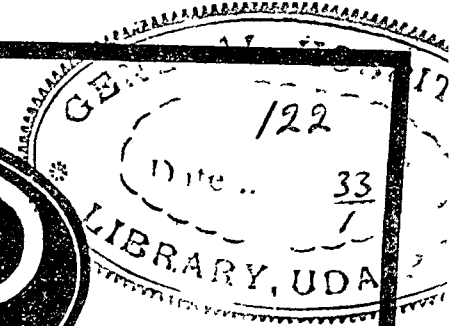
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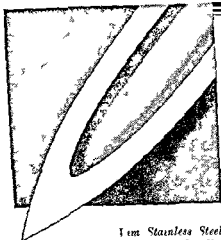
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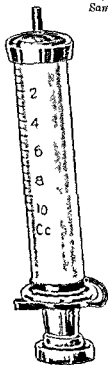


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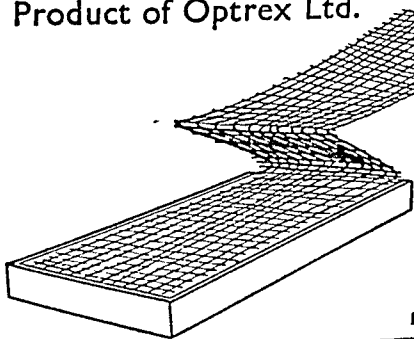
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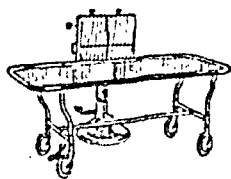
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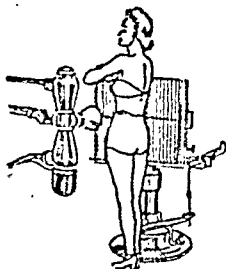
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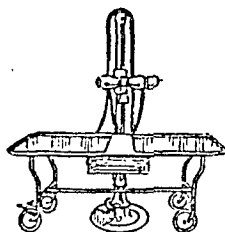
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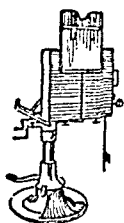
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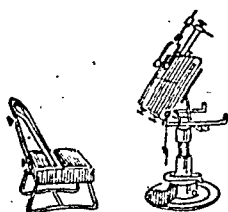
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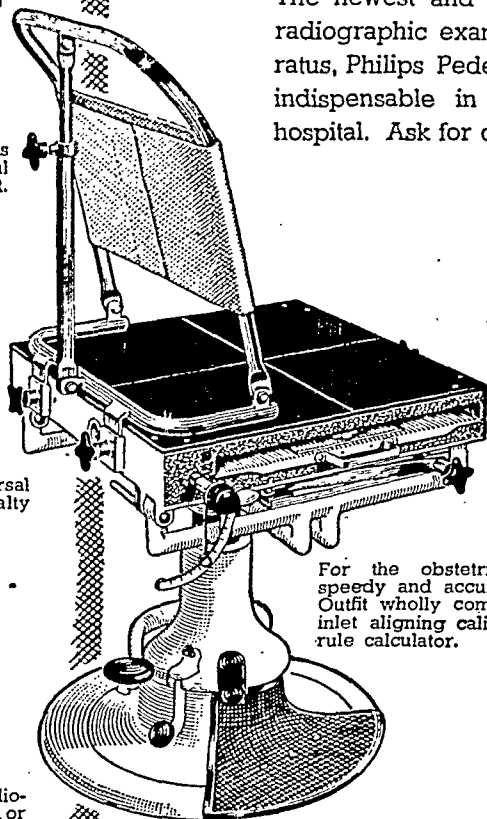
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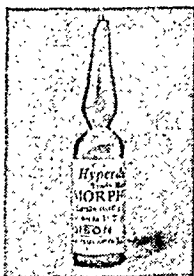


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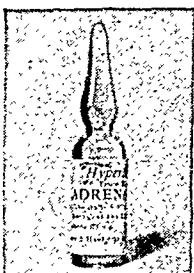
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MEDICAL PROGRESS 1946

EDITOR IN CHIEF

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PHYSICIAN TO THE KING; CONSULTING PHYSICIAN TO
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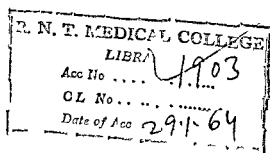
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INTRODUCTION

BY

THE EDITOR IN CHIEF

In a brief postscript to the Introduction to the 1945 volume of Medical Progress the publishers, recording the recent death of Sir Humphry Rolleston, said: "There is a simple epitaph which will for all time remain in our publishing house: 'The Rolleston tradition survives' ". It is a great thing for a man to have earned such commendation; and Rolleston did, indeed, set a standard in editorship which will make it very difficult for another to follow him. His encyclopaedic knowledge, harnessed to a careful and critical mind which was intolerant of any deviation from the accurate, made of him the ideal editor. To follow him in this present task calls for some courage.

Two more deaths are to be recorded amongst those who contributed to the Critical Surveys of the 1945 volume. Sir Arthur Hurst had already died by the time his article appeared. And now we publish another posthumous paper—that by the late Dr. R. D. Gillespie, on Mental Diseases. This article was probably Gillespie's last contribution to medical literature.

As is usual, the progress volume of this work provides the reader with three sections: critical surveys, developments in drug therapy, and abstracts. The number of critical surveys has been increased to fourteen: twelve are concerned with special fields of Medicine and two are on particular subjects, namely penicillin, and cancer. The "team" which presents these articles is representative and authoritative. We are fortunate in securing from Sir Howard Florey a full survey of our knowledge of penicillin up to the date given. Although, and inevitably, the subject is dealt with by more than one of the other writers, this epitome, and wider sweep, from one of the three men to whom we owe our knowledge of this great therapeutic advance will, we feel sure, be very welcome. Dr. Peacock's article on cancer, with its useful commentary and list of references, will be of much service to those of us who are interested in this vital subject—and which of us is not?

It may not be amiss to draw attention to the fact that in most of these critical surveys the authors—very naturally—deal *inter alia* with subjects to which they have themselves devoted attention and to which, also, they have made outstanding contributions. This, in our view, is a feature which makes the articles of exceptional value.

The section on drugs is written this year by Professor Noah Morris.

We should like to pay a tribute to the care and thoroughness with which the abstracts are written and prepared. Be it noted that they are not a mere matter of "scissors and paste": they are themselves critical surveys of current literature. They should be read and valued as non-committal epitomes of what authors who are in the van of medical progress are saying.

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MEDICINE

BY THE RT. HON. LORD HORDER, G.C.V.O., M.D., B.Sc., F.R.C.P.
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SOCIAL MEDICINE

The last year of war—total war, with its almost intolerable strain upon the individual and the Nation—has emphasized an orientation in Medicine which began to be obvious soon after the inception of the conflict: towards the group as a whole rather than towards the members of the group. We are thus faced with that aspect of our art and science which has come to be called “social medicine”. This is not to be confused with “socialized medicine” and still less with “nationalized medicine”. “Social medicine is medical science in relation to groups of human beings”, and is thus distinct from clinical medicine which is “the science of the sick individual” and from preventive medicine which is “medical science applied to the elimination of sickness by appropriate social and collective procedures”. It is concerned “especially with the study of all social agencies which promote or impair the fullest realization of biologically and socially valuable human capacities”. “Modern medicine must concern itself not merely with the alleviation of disease but must also include . . . all that pertains to man’s well-being. . . . The individual is not to be considered apart from his external world. . . . When external stress is too great the internal harmony is destroyed.” These quotations from Professor Crew help to clarify what amounts not so much to a new concept as to our “changing views concerning the nature and causation of disease”.

According to Crew the problems of social medicine are of two kinds: one defines the social environment in relation to morbidity and mortality; the other deals with the social agencies which tend to maximum health. The recent war led to rapid development in respect of both of these aspects of social medicine, for the “Army demanded . . . a corpus of knowledge concerning occupation, locality, social amenities, personal habits, aspirations, risks and responsibilities” and, although far less organized and therefore much less effective, industry, harnessed to the national effort, has seen its own branch of Medicine leap ahead. In the Army, at least, “positive health” has a real meaning, for both the psychiatrist and the expert in physical medicine have come into their own. As Crew truly observes, the combination of these two must be projected into post-war civil life so as to secure “maximum fitness for a particular job in a particular environment”. If this comes about we shall realize at last Virchow’s vision of Medicine as a social science. We shall see, in Crew’s words, “the birth of a new outlook on human affairs, a new interpretation of human relations in a free society and a new scale of social values”.

NUTRITIONAL SCIENCE

Closely linked with considerations of social medicine, because of being bound up with the national health and the level of efficiency of the citizen, are those considerations appertaining to nutrition. The recent war greatly accelerated knowledge and its application in this field. Mellanby, in reviewing the present situation of nutritional science in Medicine, issues warnings and faces the problems which await solution. He points to the danger of a specialized outlook, especially the too rapid development of a new discovery and its “adoption as a fetish by an advertisement-goaded public”. He considers that the chemist’s success has outrun that of the biologist, for although we have fairly exact knowledge of a number of essential substances in food, we do not yet know why they are essential or in what way they work. The relation of nutrition, and therefore of essential nutrients, to infection is another as yet unsolved problem; the solution will be arrived at only by keeping a balanced view of the relative importance of the two factors, infection and resistance to infection, as influ-

enced by nutrition. One of the most fascinating problems in this field is that of the extent to which dietary factors have specific anti-infective action.

Referring to the importance of implementing knowledge of nutrition during war conditions, Mellanby points out that the Ministry of Food, whilst, generally speaking, it followed the experts' advice, was guided in so doing sometimes by the exigencies of national health and sometimes by the fact that shipping and economic conditions forced the issue. It has so happened that both of these considerations have led to the same result. In the long term policy of peacetime, however, scientific and economic factors (so called) may well prove to be divergent, and "unless the nutritional needs of the people are given precedence over economic claims, much of the progress in health standards of the population may be lost."

In countries like Great Britain which are mainly industrial, two foodstuffs have special claims to national control: bread, and milk. As regards milk, determined Government action is necessary to increase the quantity and to improve the quality. As regards bread, there is almost general agreement in Great Britain that bread should be made of flour containing as much of the wheat berry as is physiologically absorbable—that is, the whole grain except for the coarse bran. In the United States of America, however, a "replacement" policy is advocated and has been in operation, whereby vitamins prepared synthetically, and also iron, are added to a low-extraction type of flour. The latter policy assumes that we know all that there is to be known about the vitamins of the wheat berry and their physiological action, which is probably far from being the truth. Seeing that the best available use of foodstuffs is one of the most important post-war issues from the international point of view, cooperation between the nations is essential, and cooperation to secure a common policy in this matter of bread will be practicable only if some such body as the Health Section of the League of Nations undertakes the task.

Platt, whose field work in the nutritional sphere during the past ten years has probably been second only in importance to that of McCarrison in the early days, reviews the aspects of research in connexion with the subject. He recognizes primary dietary diseases, such as rickets, beri-beri, scurvy and pellagra, and minor (generally multiple) dietary defects or insufficiency, as well as secondary deficiency conditions developing in connexion with other diseases or with impaired absorption or abnormally increased requirements. He points out that the grade of a deficiency disease, whether primary or secondary, depends upon the degree of the insufficiency of the food factor and its duration: the degree may be mild, moderate or severe, the duration acute, subacute or chronic. Over and above the main factor of vitamin B₁ deficiency in beri-beri, various stress factors were found to be important: physical exertion, amount of rest and sleep obtained, the quantity of carbohydrate in the diet, the temperature and humidity of the climate, the coexistence of infections (especially when pyrexial), hyperthyroidism and pregnancy. The presence of these stress factors can be recognized in the minor deficiency states to which Platt and others drew attention from 1936 onward. Platt quotes the report of the United Nations Conference on Food and Agriculture (1943) in its reference to the wartime policy pursued in Great Britain: "Recent experience has demonstrated how effective a considered food and nutrition policy, based on scientific knowledge and experience, can be in safeguarding the health of a population." He outlines the steps which are involved in drawing up a scientific food policy. They include the following: (1) Determination of the nation's needs in terms of the more important nutrients, this includes knowledge of the population distribution in respect of infants, children, pregnant and nursing women and occupational groups. (2) Translation of these needs into terms of customary foods and the approximate amounts in which they are eaten. (3) Estimation of the food supplies both from home production and from imports. (4) Comparison of the aggregate supply with the requirements based on nutritional needs, so as to detect and measure the gaps between the two and to determine how these should be filled. (5) Arrangements for ensuring equitable distribution of the supplies of food available. Platt advocates the establishment of a nutrition council in every community and of a technical panel chosen from departments of health, agriculture, education and administration. The "conception of nutritional science as the identification and study of disease due to gross nutritional deficiency has evolved through several stages to a deliberate planning of human society to ensure optimal nutrition."

CARDIOVASCULAR DISEASES

In the realm of cardiovascular diseases a few recorded observations and investigations call for comment.

Patent ductus arteriosus

Gilchrist reviews the surgery of patent ductus arteriosus and analyses a series of twenty-eight cases treated by ligation of the ductus. There were four deaths, two from the subacute bacterial endocarditis for which the operation was done and two as the result of the operation. Of the twenty-four survivors all but one showed improvement and in one case, that of a boy aged 13 years, the patient's state improved from that of a cardiac cripple to one of good health in the subsequent two years. It might be expected that the younger the subject the better the result. Tubbs, who describes the technique fully, considers that in infected cases the indication for operation is 100 per cent.

Shapiro provides us with some useful material on the pre-operative diagnosis and on the choice of suitable cases for the procedure.

The vasodilation caused by nicotinic acid medication has led to its common use in angina pectoris and coronary thrombosis. Stokes, in a series of carefully observed cases, cannot confirm that the drug has any beneficial action; indeed, its action compares indifferently with that of nitroglycerin.

Subacute bacterial endocarditis

The intriguing subject of subacute bacterial endocarditis has been re-surveyed by Willius^{1, 2, 3, 4} as regards its aetiology, morbid anatomy and symptomatology. His papers form a very useful summary, even although they do not add new facts. It is a little startling to read that rheumatic fever and subacute bacterial endocarditis are two forms of the same disease; the evidence given seems to be very inadequate. In this section on symptoms Willius stresses the frequency and variety of the neurological manifestations, and the importance of these can be attested by those who have had much experience of the protean nature of the way in which endocardial infection expresses itself.

A *résumé* of the results of modern chemotherapy has recently been given by Dolphin and Cruickshank. They point out that, despite optimistic early reports, the sulphonamide group of drugs, even when exhibited in conjunction with heparin, were almost entirely ineffective against *Streptococcus viridans* endocarditis. In this connexion they repeat the old warning against carelessness in diagnosis and especially emphasize the known importance in this regard of arterial embolism. Temporary control of the bacteriaemic part of the disease process, with remission of pyrexia and some alleviation of symptoms, has been a common experience, but the subendothelial colonization, which is the essence of the whole pathogenetic process, remains unaffected and serves to re-infect the blood stream later. Even in acute (bacterial) endocarditis sulphonamide therapy fails in the majority of cases.

The authors then consider the results of penicillin treatment. In subacute bacterial endocarditis the results were, in the earlier cases, mainly unsuccessful. Later workers, however, using daily doses of 200,000 units with or without heparin, obtained much more satisfactory results. As we know, a chosen team of workers in British hospitals (under Professor Christie) is at present engaged in verifying these and in extending the investigation. In acute bacterial endocarditis a number of "cures" have resulted from the use of penicillin (Keefer and his colleagues; Loewe and his colleagues). The present authors report on a series of six cases, giving convincing evidence of differential diagnosis and details of treatment. In three cases the infection was by *Streptococcus pyogenes* group B, in two by *Staphylococcus aureus* and in one by *Streptococcus pyogenes* group A. Of the six patients, four were alive between six and twelve months after treatment was stopped, three were well and one had improved.

Loewe's^{1, 2} review of the subject of the "combined use of anti-infectives and anti-coagulants in the treatment of subacute bacterial endocarditis" concludes with the optimistic remark that "if the patient is in good physical condition, the duration of the disease less than 3 months, and the causative organism sensitive to penicillin, a satisfactory result may be anticipated, barring accidents, in virtually every case".

The trouble is that in a considerable proportion of cases some of these criteria are not satisfied

Hypertension and arteriosclerosis

The aetiology and treatment of hypertension continue to attract attention. The use of potassium thiocyanate has been followed by toxic symptoms and even by fatality, and these results have tended to reduce the trials that would otherwise be given to it. Koffler, Freireich and Silverman consider that the ill effects can be avoided by estimating the blood levels of the drug, since these are found to vary considerably when the dosage by mouth remains the same. In the meantime we must reluctantly regard this drug as one of those of modern introduction of which the practitioner fights shy because he does not have proper control in its use.

Smithwick analyses 156 cases of essential hypertension in which the patients were treated by splanchnicotomy and were observed over a period of from one to five years. This author recognizes three types among these cases: (1) those individuals in whom the pulse pressure was less than half the diastolic pressure, (2) those in whom it was at some figure up to 19 millimetres more than half the diastolic pressure, and (3) those in whom it was 20 or more millimetres greater. The operation results were best in the first group and worst in the third. The best results of all were in the women of group (1), the worst were in the men of group (3). Careful perusal of Smithwick's paper gives some help in the selection of this—granted bold—procedure in a disease the seriously progressive nature of which justifies its consideration.

The problems of arteriosclerosis continue to prove to be baffling. A thoughtful paper, however, by G. Evans, who has contributed so much of late years to our study of the matter, merits attention. This authority defines the condition as "a vascular reaction in terms of structure to a pathogenic stress." Evans considers that persistent hypertension is clinical evidence of arteriosclerosis. He considers that figures of the blood pressure range 240/130 millimetres lead to progressive changes, whereas those of 200/100 are compatible with quiescence of the disease and years of active life. We are exhorted to attend to the signs which precede evidence of organic disease and which (Evans thinks) indicate local angiospasm: nocturnal cramps, preceding intermittent claudication, tachycardia with slight dyspnoea and pain in the cardiac field, haemorrhages and exudates in the brain, retina, nose, kidneys, stomach, bowel, lungs and uterus.

Rosenbluth considers that in every case of hypertension primary renal disease should be excluded because of the possibility that the kidney trouble may be unilateral and amenable to surgery. He thinks that in most cases it is not necessary to try to reduce the arterial tension. He believes that psychotherapy has a place in treatment, whether by removing "some neurotic mechanism" or by helping the patient to adjust himself to the limitations imposed by the disease.

THE RHEUMATIC DISEASES

"The four main clinical and pathological forms of rheumatism are rheumatic fever, the rheumatoid type of arthritis, the osteo-arthritic type and non-articular rheumatism or fibrositis" (Bach). This is a convenient and generally accepted division of the subject and will serve sufficiently for the following *résumé* of some recent observations in this field.

Rheumatic fever

Aetiology.—The aetiology remains obscure. The trend of opinion is perhaps towards a virus infection, with an allergic state as next favourite, either being activated—although not always necessarily so—by a previous, rather than concurrent, infection with haemolytic strains of streptococci. Copeman adduces evidence that the preceding infection may be of other than streptococcal nature, for instance dysentery or malaria. The problem has come to the fore on account of outbreaks of the disease in the United States fighting forces and in British training ships. Morris and Titmuss² have stressed the predisposing factor of crowded and perhaps ill ventilated living conditions (Leading Article). Coburn and Moore consider that, regarded patho-

genetically, there are three phases in the sequence: (1) of streptococcal infection, (2) of quiescence, (3) of rheumatic fever.

Copeman reports on the result of an attempt to transmit rheumatic fever to a group of five volunteers by the injection of blood from a patient who had the disease. In two volunteers mild attacks of the disease developed. The pooled blood for these two cases was passed on, on the third day of the development of their symptoms, to four other volunteers. In one of these symptoms developed. The blood of this patient was again injected into four volunteers; in one of these something comparable with rheumatic fever developed, including an apical systolic bruit. Passage from this patient was without effect.

Diagnosis.—When the disease was much more common in civil life this was not difficult, the clinical picture, together with the result of salicylate medication, leaving little doubt about the nature of a child's or young adult's illness. Of late, however, with decreasing incidence, the picture is less frequently recognized and there has undoubtedly been some change in the common features of the disease; pericarditis, especially with effusion, for example, is nowadays quite uncommon. Although they are non-specific, any two of the following conditions are regarded by Jones as diagnostic when they are present together with any combination of carditis, arthralgia, chorea and nodules: fever, abdominal or praecordial pain, erythema, epistaxis, pulmonary changes, anaemia, leucocytosis, and raised blood sedimentation rate. Jones considers that the three diseases which are likely to cause most confusion are (1) Still's disease, (2) disseminated lupus erythematosus and (3) acute rheumatoid arthritis. Less often the disease is to be differentiated from tuberculosis, undulant fever, meningococcal and gonococcal septicaemia and gout.

Berger renews attention to the occurrence of peritoneal symptoms, which not seldom simulate appendicitis. In the course of laparotomy in one such case, the peritoneal surface of the appendix was found to be inflamed but not more so than were the ileum and the peripheral peritoneum. Cultures were sterile.

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The above results are confirmed by Coburn and Moore, by Kuttner and Reyersbach, and by Thomas and France. A thorough trial of penicillin, however, during phase (3), that is, during the actual course of the rheumatic fever, has been quite ineffective; like the sulphonamides it may even aggravate the attack. Eight cases were treated by Watson, Rothbard and Swift—two by intramuscular injection, four by intravenous injection and two by continuous drip. The treatment was continued over a period of two weeks, but it failed to alter the course of the disease.

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The use of sodium salicylate has come under review and, characteristically, the drug has been "pushed" to extreme limits with the object of estimating its potentialities. Coburn has given it in very large doses intravenously with rapid results as regards symptoms and blood sedimentation rate. Ashworth and MacKenzie, however, have reported intense toxic symptoms from such mass dosage: haemorrhages, vertigo, deafness. They suggest the use of vitamin K as a protective agent, should this method be employed.

Rheumatoid arthritis

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The trouble is that in a considerable proportion of cases some of these criteria are not satisfied

Hypertension and arteriosclerosis

The aetiology and treatment of hypertension continue to attract attention. The use of potassium thiocyanate has been followed by toxic symptoms and even by fatality, and these results have tended to reduce the trials that would otherwise be given to it. Koffler, Freireich and Silverman consider that the ill effects can be avoided by estimating the blood levels of the drug, since these are found to vary considerably when the dosage by mouth remains the same. In the meantime we must reluctantly regard this drug as one of those of modern introduction of which the practitioner fights shy because he does not have proper control in its use.

Smithwick analyses 156 cases of essential hypertension in which the patients were treated by splanchnicotomy and were observed over a period of from one to five years. This author recognizes three types among these cases: (1) those individuals in whom the pulse pressure was less than half the diastolic pressure, (2) those in whom it was at some figure up to 19 millimetres more than half the diastolic pressure and (3) those in whom it was 20 or more millimetres greater. The operation results were best in the first group and worst in the third. The best results of all were in the women of group (1), the worst were in the men of group (3). Careful perusal of Smithwick's paper gives some help in the selection of this—granted bold—procedure in a disease the seriously progressive nature of which justifies its consideration.

The problems of arteriosclerosis continue to prove to be baffling. A thoughtful paper, however, by G. Evans, who has contributed so much of late years to our study of the matter, merits attention. This authority defines the condition as "a persistent hypertension is clinical evidence of arteriosclerosis. He considers that figures of the blood pressure range 240/130 millimetres lead to progressive changes, whereas those of 200/100 are compatible with quiescence of the disease and years of active life. We are exhorted to attend to the signs which precede evidence of organic disease and which (Evans thinks) indicate local angiospasm: nocturnal cramps preceding intermittent claudication, tachycardia with slight dyspnoea and pain in the cardiac field, haemorrhages and exudates in the brain, retina, nose, kidneys, stomach, bowel, lungs and uterus.

Rosenbluth considers that in every case of hypertension primary renal disease should be excluded because of the possibility that the kidney trouble may be unilateral and amenable to surgery. He thinks that in most cases it is not necessary to try to reduce the arterial tension. He believes that psychotherapy has a place in treatment, whether by removing "some neurotic mechanism" or by helping the patient to adjust himself to the limitations imposed by the disease.

THE RHEUMATIC DISEASES

"The four main clinical and pathological forms of rheumatism are rheumatic fever, the rheumatoid type of arthritis, the osteoarthritic type and non-articular rheumatism or fibrositis" (Bach). This is a convenient and generally accepted division of the subject and will serve sufficiently for the following *resumé* of some recent observations in this field.

Rheumatic fever

Aetiology—The aetiology remains obscure. The trend of opinion is perhaps towards a virus infection, with an allergic state as next favourite, either being activated—although not always necessarily so—by a previous, rather than concurrent, infection with haemolytic strains of streptococci. Copeman adduces evidence that the preceding infection may be of other than streptococcal nature, for instance dysentery or malaria. The problem has come to the fore on account of outbreaks of the disease in the United States fighting forces and in British training ships. Morris and Titmuss² have stressed the predisposing factor of crowded and perhaps ill-ventilated living conditions (Leading Article). Coburn and Moore consider that, regarded patho-

genetically, there are three phases in the sequence: (1) of streptococcal infection, (2) of quiescence, (3) of rheumatic fever.

Copeman reports on the result of an attempt to transmit rheumatic fever to a group of five volunteers by the injection of blood from a patient who had the disease. In two volunteers mild attacks of the disease developed. The pooled blood for these two cases was passed on, on the third day of the development of their symptoms, to four other volunteers. In one of these symptoms developed. The blood of this patient was again injected into four volunteers; in one of these something comparable with rheumatic fever developed, including an apical systolic bruit. Passage from this patient was without effect.

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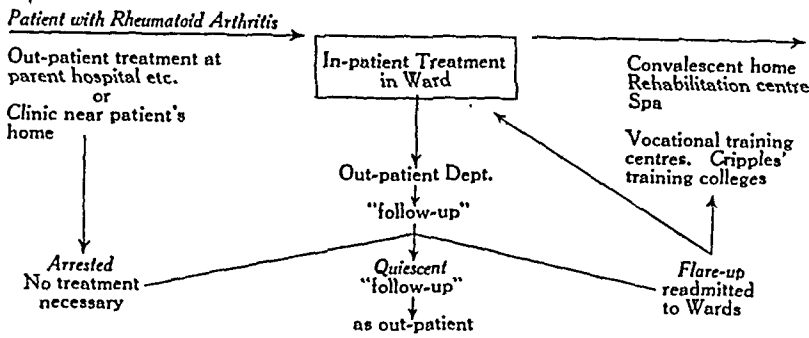
Rheumatoid arthritis

Almost nothing informative, or even suggestive, has of late been advanced on the

aetiological side. In treatment, the inevitable trial of penicillin has been made by Boland, Headley and Hench, in ten soldiers with early progressive disease. The result was quite neutral in seven cases, showed aggravation of symptoms in one, showed subjective, without objective, improvement in one, and both subjective and objective improvement in one. No definite improvement took place in the blood sedimentation rate. The authors consider the results to be essentially negative. In view of the small number of cases treated it may be well to re-survey the method when supplies of the remedy are more available. Douthwaite reports the results of treatment with bismuth as an alternative to gold. Of twelve patients (coming for treatment consecutively) six lost their symptoms, but in two of these relapse took place after a few weeks; the remainder showed no improvement. No toxic symptoms were produced, although the dosage chosen was apparently adequate. The metal was used in nine cases, the salicylate in three. In three of the cases gold treatment employed previously had failed, bismuth also failed in these.

Bach contributes a very useful scheme under the heading, "The Management of Rheumatoid Arthritis", illustrating well the protean nature of the known factors entering into the pathogenesis of the disease and also the team work necessary for the investigation and treatment of the patient. (See Charts 1, 2, 3.)

CHART 3



In the following table Bach summarizes the main features of his own plan of treatment.

TABLE

IN-PATIENT TREATMENT

Preliminary investigation—Clinical, Radiological, Pathological

Treatment	
(1) Rest	psychological, physical
(2) Drugs	(a) to relieve pain, muscle spasm and promote sleep Salicylates, amidopyrine, Prostigmin, Amytal etc. (b) to treat anaemia and hypochlorhydria Iron, hydrochloric acid dil, liver extract (c) to stimulate "reticulo-endothelial system" Gold preparations (Myocrisin, Solganal etc.) bismuth preparations
(3) Endocrine preparations	Oestroform, testosterone propionate, thyroid, suprarenal, insulin
(4) Vitamin preparations	Nicotinic acid, Benerva Ascorbic acid, Radiostol, Multivite
(5) Diet	High calorie, salt free, small bulk, appetizing to increase calorie value and correct vitamin deficiency
(6) Physical treatment to prevent or correct deformity	Relaxation and breathing exercises (individual or group), slings, springs, pulleys Infra-red, ionization, short wave, U.V.L., mud, pool etc. Corsets, foot supports
(7) Orthopaedic measures	Splinting with plasters to correct or prevent knee, wrist deformity etc. Joint aspiration, lavage, capsulectomy etc.
(8) Treatment of possible foci of infection	Teeth, sinuses, gallbladder, pelvic organs etc.
(9) Special measures	Blood transfusion, "therapeutic jaundice", splenectomy, sympathectomy
(10) Occupational therapy	Remedial specific, non-specific, diversional
(11) Advice on course of disease, how to modify it, where to get treatment, "follow-up", "Rheumatic Club" etc.	

Osteoarthritis

In a useful paper Neligan makes a timely contribution to this subject and comments upon the "air of frustration" with which the condition is so frequently regarded, owing to the idea that it is a "degenerative condition, the result of wear and tear on ageing tissues". Injury he regards as an invariable causative factor, although he admits that this may be no more than "ordinary use in susceptible joints". Importance is attached to the getting of intelligent cooperation from the patient and to sparing the joints affected, by rest, by modified activity and by weight reduction. The treatment of obesity, when present, may have dramatic effect. Menopausal arthritis reacts well to treatment. Function should be maintained and for this active stretching of the joint and active training of special muscle groups may be demanded. Application of heat is nearly always helpful. The chief indication for massage is fibrositis of the muscles and joint capsule. When pain is severe an effort should be made to find its immediate cause: periarticular fibrositis, synovitis, loose bodies or fringes, muscle spasm, extensive erosion. Persistent pain is unusual; its presence should suggest added infection, fracture, osteomyelitis, Paget's disease or a growth. Operative measures are to be considered in intractable cases.

The indications for "nail arthrodesis" for osteoarthritis of the hip are considered by Watson-Jones to be unilateral disease with severe pain, movement restricted to

30-40° and inability to walk more than one mile. For athroplasty this authority considers the indications to be bilateral disease with the same disabilities.

Fibrositis

Recent tentative views on the nature and aetiology of this elusive condition are dealt with in an interesting *Lancet* annotation. Elliott's demonstration that the tender spots in sciatica were expressions of a central (segmental) cord excitation, due to irritation of nerve roots, is considered to have brought the subject into a new perspective. Reference may be made to the work of Copeman and Ackerman, who suggest that small local fatty hernias may form in connexion with the muscle fasciae and later become fibrosed. They adduce post mortem evidence in support of this view.

PEPTIC ULCER

A number of considerations combine to make the subject of peptic ulcer one of continuous interest: its frequency, its economic aspects, the gaps in our knowledge of its aetiology and the lack of uniformity in the view of experts concerning treatment.

Incidence

Tidy has examined the admissions to St Thomas's Hospital, London, between 1910 and 1913 and between 1927 and 1937, in order to obtain indications of the main trends. The analysis is very thorough but the interpretation is difficult. The inference is that more than one group of aetiological factors is at work and that these operate in varying intensity at different ages and in the two sexes.

Mortality in Great Britain

Morris and Titmuss¹ report that this increased during the ten years just preceding the recent war and still more after its outbreak. Between the ages of 45 and 75 years mortality was doubled. In women the increase was less at all ages under 55 and was relatively small at the ages between 55 and 75. In gastric ulcer occurring under the age of 55 years the mortality rose as the social scale descended, but this was not so in the case of duodenal ulcer. At ages over 65 years there was an increased mortality in the well to do and professional classes, at 70 and over the increase was twice as great. In London the mortality was 100 per cent higher than it was in rural districts. Here again, therefore, evidence tends to show that there is a variety of factors in pathogenesis and mortality.

Some factors in pathogenesis

The question of trauma was investigated by Gray and was found not to be negligible. Bird, Limper and Mayer (quoted by Aaron) find the disease to be not rare in children, in whom it is of the "acute" variety when occurring in those under 7 years of age, in children between the ages of 7 and 15 it has the same features as it has in adults. Blum finds only fifteen cases of peptic ulcer of the greater curvature in the literature and considers that a suspicion of malingerer always attaches to the lesion when it is found in this situation. Palmer (quoted by Aaron) regards as reliable the evidence that a malignant ulcer may heal in the first instance.

Of the accepted causative factors much attention has been paid to those of a psychosomatic nature, and it is clear that Wolf and Wolff's work upon their patients who had a herniated portion of stomach has had nearly as much influence on physicians as the classical observations of Alexis St Martin have had on physiologists. These observers found that emotions of resentment, hostility, anxiety and aggressiveness led to hypersecretion, hypermotility, congestion and even superficial ulceration, whereas secretion was controlled by the sight and smell of food and by its presence in the small intestine. This has led to a more frequent and studied psychiatric approach in treatment, and also to the favouring of sedative drugs with the object of imposing a "psychologic block", these even ranking in the minds of several writers before alkalis and adsorbents.

Diagnosis

St John, Swenson and Harvey investigated with the fluoroscope the stomach and duodenum of 2,413 persons who were symptomless. The results were surprising,

54 cases showing a deformed duodenal cap, 2 carcinoma, 25 diaphragmatic hernia (in two cases "very large"), 7 cardiospasm, 1 lymphosarcoma and 1 polyp. The authors naturally raise the question of a fuller application of the method, in order both to install a suitable regimen in the cases of peptic ulcer and to secure diagnosis of cases of gastric cancer at an earlier stage than is usual.

H. Evans doubts the value of test meals and laments the waste of time spent upon them. Neither the pre-ulcer nor the pre-cancer lesions favoured by the late Sir Arthur Hurst have received confirmatory recognition by more recent observers. Indeed, the whole subject of "gastritis"—an extremely difficult one in view of the known variations in the degree of both the rugosity and the congestion of the gastric mucosa under varying physiological conditions—awaits further elucidation. Cordiner summarizes the x-ray findings obtained by his "mucosal relief pattern" but exercises great forbearance in their interpretation. He thinks that it is possible to diagnose hypertrophic gastritis only when polypoid hypoplasia is present; in atrophic gastritis he frankly considers that diagnostic characters cannot at present be established. Strict correlation of gastroscopy with histological examination is probably the most promising field, and here Hancock has described the results in fifty cases.

Treatment

Medical treatment.—If the view be taken that peptic ulcer is a disease in which the ulcer is an incident, it is clear that treatment should begin before ulceration appears, not with its appearance. Whether the pre-ulcer stage be termed "acid dyspepsia" or "hyperchlorhydria", or be given some other name, does not matter so much as does the recognition of the clinical type of gastroduodenal dyspepsia concerned. Even if x-ray examination reveals no crater, the presence of persistent spasm and of rapid emptying, in a patient who presents the recognized clinical syndrome, calls for treatment on lines which are fairly established and generally accepted in the treatment when ulceration has been demonstrated. Collins summarizes these lines as follows: frequent meals, the avoidance of condiments and of alcohol, adequate guidance on the psychological side, and the giving of sedatives, alkalis, adsorbents and anti-spasmodics. As sedative he chooses sodium phenobarbitone (soluble phenobarbitone), $\frac{1}{2}$ grain, two or three times a day; as alkali: calcium carbonate, 15 grains, three times a day before meals; as adsorbent: aluminium hydroxide, 10 grains, three times a day between meals; he gives belladonna, $\frac{1}{8}$ grain, before meals, "to dryness". H. Evans enters a plea for iron and ascorbic acid and thinks the use of a sedative to be more important than administration of alkalis. Morlock advocates aluminium hydroxide gel and magnesium trisilicate, and agrees about the value of sedatives. In regard to the important matter of diet, opinion is fairly general that the very strict feeding (really starving) of some years ago was not helpful (except for three or four days after severe haemorrhage) and that the Sippey and Lenhartz diets were also on the *maigre* side. There is a growing tendency to vary the diet according to the individual case. Garbat gives the following scheme, which is useful and which probably conforms very closely to the practice of most physicians. For 3 days, milk; for 3 days, eggs, custard and junket; for 3 days, cooked cereals; for 3 days, cream soups, for 3+ days, bread; for 3+ days, *purée* of vegetables; for 3+ days, fish; for 3+ days, chicken; for 3+ days, lamb, ham, chopped beef; for 3+ days, *purée* of fruit.

Surgical treatment.—The indications for this treatment have settled down fairly consistently to the following: perforation, repeated haemorrhage, pyloric obstruction, suspected cancer, intractability to medical care and what Aaron terms "revamping" of previous surgery. The early resumption of essential work, however, may determine the issue in the case of certain patients; so also may conditions of life, especially in the way of feeding. Walton's unusually large experience leads him to the view that the one indication for surgery is the failure of medical treatment, and he points out that stenosis, haemorrhage, and even perforation provide evidence that the ulcer has not been cured medically. In dealing with the important matter of gastroduodenal ulcer after posterior gastro-enterostomy, he comments on the high degree of its incidence as reported from the United States of America and from Europe (30–35 per cent) and on the influence that this high figure may have had upon British surgeons in their preference for partial gastrectomy in duodenal ulcer. Walton's own figure is not higher than 5 per cent. He thinks that for patients in whom the ulcer had started early in life and for those with an unusually high acidity this serious

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SURGERY

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The figure of Lister on the cover of the penicillin number of the *British Journal of Surgery* for August 1944 brings to mind the long and often bitter controversy which has been carried on for three-quarters of a century over the value of antiseptics in surgery. The early opposition to listerism in Great Britain rested on the question: Were bacteria in fact pathogenic in the true sense of the term and did the destruction of them really amount to unjustifiable interference with the natural process of healing by the production of laudable pus? Yet at the same period a number of surgeons in Europe had adopted what they understood to be Lister's methods with zeal and enthusiasm so excessive that harmful effects, particularly carboloria, were being produced on the body as a whole.

What may be described as the lesser degrees of injury from the misuse of antiseptics—which although less obvious were no less important in their ill effects upon the wounds themselves—were not generally recognized until later, and the name of Almroth Wright will ever be associated with the doctrine that a good antiseptic must kill organisms without being at the same time an embarrassment to the leucocytes and other tissue cells which are taking part in the process of healing the wound. Fleming himself has never tired of demonstrating by experiments as ingenious and simple as they are convincing, that antiseptics of the order of phenol will kill leucocytes before they kill bacteria.

By the end of World War I the pendulum had made the full swing away from the use of chemical antiseptics: many surgeons relied entirely upon careful excision and used nothing but physiological saline to wash the wound surfaces. For late wounds with established infection the choice varied between B.I.P.P. (bismuth iodoform paraffin paste) which, when used precisely as Rutherford Morison directed, gave excellent results, Dakin's solution, which was shown to be harmless to leucocytes, and a dilute solution of acriflavine, which actually possesses more virtues than are commonly attributed to it.

The surgery of peacetime is naturally less interested in antiseptics, and the opinion that they were unnecessary if the surgery itself were of a high enough standard held sway until the advent of sulphanilamide. Here was a drug which, if used in powder form with proper care and judgment, would not interfere with the healing of a wound, but there was danger also in that the inexperienced might be tempted to rely upon the antiseptic to do all the work for them, thus undermining the paramount importance of painstaking excision. Surgery owes a debt to the teachers at home who during the recent war declined to make use of sulphanilamide as a routine, and thus proved to their students and assistants that it is possible in early wounds to obtain healing by first intention by excision alone and without the introduction of antiseptics as a prophylactic measure.

In the field conditions are different, and the need for antiseptics in both prophylaxis and treatment of established infection is everywhere evident. It must be emphasized, however, that the danger of undue reliance upon antiseptics has been so thoroughly countered by those directing military surgery, that the excellence of the primary treatment of wounds is apparent to all who have to deal with casualties at any stage of convalescence, and from any battle front.

PENICILLIN

The situation was therefore well in hand and ripe for Florey's introduction of penicillin, a drug which is an ideal antiseptic, is active in incredibly high dilutions, and is non-toxic to leucocytes. When it was first introduced penicillin was in such short supply

that it could be issued only to those who were able to use it under research conditions, and even then only for special infections. It is now more plentiful, and as it becomes more and more readily available for general use, it is advisable that the uses and limitations of the drug should be more commonly known so that uncontrolled medication may be avoided.

However plentiful the supply, penicillin should be used only after the infecting organism has been shown to be sensitive, the sole exceptions being in prophylaxis before and after operation, as an emergency measure in the early stage of septicaemia before the organism has been identified, and in the treatment of streptococcal and pneumococcal infections which fail to respond to sulphonamide treatment. The resistance of *Bacillus coli*, *Bacillus typhosus* and *Bacillus paratyphosus*, *Pseudomonas pyocyanea*, *Proteus*, and *Streptococcus faecalis* to penicillin is well known, but it is not always recognized that some strains of *Streptococcus viridans* and a few staphylococci also are insensitive.

In the early days mistakes were made in the use of penicillin owing to lack of knowledge of its properties, but thanks to the good organization set up in the Forces and in the Emergency Medical Service for instruction of pathologists and "penicillin officers", the necessary safeguards to ensure the efficacy of the drug have become widely known. Salts of penicillin even in powder form are more unstable than are other drugs in common use; they are readily destroyed by acid and alkali and by heavy metals, alcohols and oxidizing agents. Most of the common antiseptics are included in these categories, and therefore penicillin should be used by itself—save for the admixture of sulphathiazole powder which is necessary when the drug is to be dusted or insufflated on a wound surface. Since penicillin loses its activity when it is heated above body temperature it must be stored in a refrigerator, and as it is rapidly destroyed by penicillinase formed by many airborne bacteria it must be dispensed under conditions which will ensure its sterility.

Although reports are appearing of the successful treatment of gonorrhoea with penicillin given by the mouth, it has generally been administered either by local application as powder or in solution to fresh wounds, or by intramuscular or intravenous injection. Penicillin is rapidly excreted in the urine and therefore it is more difficult to maintain the necessary concentration when the drug is given intravenously. Even when it is administered by the intramuscular route the exact method used has an appreciable effect on the dosage necessary to keep the concentration up to the bacteriostatic level in the blood. If injections are given 4-hourly the dose will have to be 100,000 units, if 3-hourly, 25,000 units, and if 2-hourly, 10,000 units; therefore for economy's sake as well as for the recipient's comfort it has become the common practice to give a continuous intramuscular drip, by which method a dose of 100,000 units every 24 hours is found to be adequate. Now that it is possible to make up concentrated solutions, no more than 100 cubic centimetres of fluid need be injected per day, and if it is more convenient even smaller quantities of stronger solutions can be used. Many ingenious mechanisms have been devised for continuous administration of these comparatively small volumes of fluid (McAdam, Duguid and Challinor; St. Hill; Last), of which the Edinburgh Eudrip No. 1 apparatus seems to be the most popular.

Penicillin was at first thought to be merely bacteriostatic, but it is now believed that it kills organisms in their phase of multiplication. It can pass rapidly into the fluid of ascites and oedema but, since it is very slow in reaching the cerebrospinal fluid and the pleural and joint cavities, the only effective method of treating infection in these situations with penicillin is by aspiration and direct injection.

The dramatic effect of penicillin in septicaemia and more particularly in local acute infections such as the early stage of osteomyelitis, has prompted the happy thought that soon the surgeon's occupation may be gone. In fact the exact opposite is true—penicillin is opening up new fields for surgical enterprise and is making possible many procedures previously doomed to failure on account of infection.

A striking example of this is the success of early closure (delayed primary suture) of battle wounds. It is only fair to state that local application of acriflavine solution or the more recent proflavine-sulphathiazole powder was successfully used for such a purpose before penicillin was available, and that these substances maintain their usefulness against organisms not sensitive to penicillin. It cannot be denied, however, that the advent of this latest antiseptic has given surgeons so much confidence that

the whole attitude to the early treatment of wounds has changed. It used to be dangerous to tamper with a wound after the first twenty-four hours for fear of spreading infection, and thus application of closed plaster and perhaps a late attempt at secondary suture became the approved method, the resultant healing time was reckoned in weeks. Now, however, wounds from four to seven or ten days old can be freshened by the removal of any tags of dead tissue remaining after the primary excision, and if the wounds look healthy they may be closed completely, penicillin (or sulphonamide for penicillin insensitive organisms) being administered locally and if necessary parenterally for the purpose of controlling the residual infection. Healing time is thus reduced to a matter of days, the process being accelerated not only by bringing the wound edges into apposition but also because closure is the best safeguard against secondary infection.

Chronic osteomyelitis is another disease which, in spite of the handicaps and inconveniences which must be endured by a patient with an old discharging wound, was usually treated by the prudent surgeon with masterly inactivity. By giving penicillin systemically for some days before and after operation even these patients may be made safe for surgery, old sclerosed bone and scar tissue may be radically excised without fear of spreading infection and a healthy base may thus be prepared for subsequent grafting of bone and skin to fill the gap and close the wound.

Sometimes the local spread of an acute infection may overwhelm a patient and deny the surgeon any opportunity of coming to his aid. If the infection can be controlled, however, penicillin may give the surgeon his chance. For example, a woman swallowed a fragment of rabbit bone which pierced her oesophagus and she became so profoundly ill as a result of the pneumothorax and mediastinitis which ensued that the usual fatal result seemed to be inevitable. With penicillin, however, the fever was controlled, and the patient's general condition improved sufficiently to permit of thoracotomy, suture of the perforation and recovery (Edwards).

With increase in the available supplies of penicillin has come simplification in the methods of its administration. As mentioned above, it may be given by the mouth, and provided that special precautions are taken to prevent its destruction in the stomach, an adequate concentration can be maintained in the blood. The local antiseptic action of penicillin pastilles has proved to be of great value in the treatment of throat infections (MacGregor and Long).

WOUND HEALING

Steady progress is being made towards a fuller understanding of the nutritional factors involved in the healing of wounds, but such considerations must not detract attention from local treatment. The importance of infection in granulating wounds must never be forgotten, and as soon as a judicious use of the appropriate antiseptic has had its maximal effect, secondary closure should be carried out in order to prevent reinfection (Patrick). This may involve quite an extensive operation, freshening of the wound by excision of its edges and the granulation tissue in its base, undercutting of the skin, and if necessary fashioning of flaps or placing of skin grafts so as to achieve closure without tension. Although the method was in common use at the end of World War I, it is significant that so important an aid to shortening of the healing process has had to be recovered from the limbo of half forgotten experiences.

When secondary closure is inappropriate, the growth of epithelium must be encouraged. Excessive formation of granulation tissue which antagonizes epithelial growth, and infection which kills young epithelial cells, must first receive attention, but if the wound remains indolent, assistance may be obtained from the local application of growth promoting substances. The results obtained by Kerr and Werner with heart extract powder prepared by Doljanski are striking enough to encourage further research along similar lines.

The problem of stimulating tissue repair arises chiefly in wounds of long standing, since the natural process of healing in fresh clean wounds scarcely calls for improvement. Yet in all wounds, before fibroplasia is established, there is a lag period of some days in which, in the absence of fibroblasts and collagen, edges and surfaces are easily separated. This early period of instability may be shortened by promoting the formation of fibrin to glue surfaces together and to provide a scaffolding on which

fibroblasts may build themselves up. Many ingenious suggestions have been made for the production of such a fibrin layer, and about the uses to which it may be put.

Skin grafts can be stuck firmly in position within a few minutes, and the fibrin can be made from the patient's own blood (Sheehan). Ten cubic centimetres of blood is centrifuged in a sterile tube with 1 milligram of heparin and 1 cubic centimetre of Tyrode's solution. The plasma is pipetted off and the leucocytes are scooped off the top of the erythrocytes and put in another tube with 1.5 cubic centimetres of Tyrode's solution; some glass beads are added for the purpose of breaking up the cells when the tube is shaken. The recipient area is painted with plasma which contains fibrinogen; the under surface of the graft is painted with the broken up cells which provide thrombin to convert the fibrinogen into fibrin when the two surfaces are brought into contact. The firm adhesion satisfies the most essential condition to ensure the "take" of a graft: close apposition and the absence of any collection of exudate or blood beneath the graft.

Stock pooled plasma and commercial thrombin solution in isotonic saline may be employed if it is inconvenient to prepare these substances from the patient's blood, and the rapidity of clotting may be varied by altering the strength of the thrombin solution (Young and Favata). If wound surfaces are moistened with plasma and are then sprayed with thrombin, the wound edges have merely to be held together for about two minutes when, provided there is no tension, the closure is permanent. The method is advocated particularly in order to avoid subcutaneous collections of exudate under extensive skin flaps, as for example after radical mastectomy.

Another use for fibrin is in the arrest of haemorrhage, especially in neurosurgery (Ingraham and Bailey). Fibrin foam, in texture like a delicate honeycomb, cut into small pieces and soaked in thrombin solution, when held in contact with a bleeding point quickly controls the haemorrhage from dural sinuses and cerebral veins or the oozing from cut surfaces of the brain. It is to be preferred to muscle strips, and can be used in places where electrocoagulation would be dangerous. Fibrin foam is not recommended for the arrest of arterial bleeding.

The same material in thin sheets may be used for patching gaps in the dura, and it is alleged that in the process of organization it does not become adherent to the cortex. For the same reason it will prove to be of value in the repair and grafting of peripheral nerves (Woodhall).

PILONIDAL SINUS

Pilonidal sinus, in spite of its bad reputation for tardy healing after excision, was formerly regarded as a comparatively trivial malady. War has transformed it into a condition of major importance, partly because its incidence is greater than might have been expected, but chiefly because the prolonged absence from duty during treatment—often amounting to about three months—has an appreciable effect upon manpower. It is only natural, therefore, that a large number of papers should have appeared recently on this subject, most of which have as their chief object the advocacy of methods whereby the time under treatment may be shortened.

It has long been known that these sinuses occur four times more often in men than in women, and that injury provokes the suppuration which first draws attention to an abnormality which has been present since birth. It is not surprising, therefore, that inflamed pilonidal sinus has been named "jeep disease". It is of interest that although the sufferers are commonly dark-haired and hirsute individuals, some dark-skinned races, including the Negro and the North American Indian, are almost exempt from the disease.

The principles of treatment are three: preliminary evacuation of accumulated debris and pus, complete excision of the epithelial-lined sinus and all extensions therefrom, and abolition of the resulting dead space. The initial treatment of suppuration is clearly necessary in order to prevent as far as possible an infection which will inevitably interfere with sound and rapid healing of the operation wound. There is, however, another equally important reason for establishing drainage and for waiting until the signs of surrounding inflammation have completely subsided: the bleeding from hyperaemic tissue around the sinus may prove to be uncontrollable, and the resulting haematoma spells disaster. A period of about six weeks must often elapse between drainage and excision if such a complication is to be avoided.

To ensure complete excision of the sinus is not an easy matter because of the multiple tracks which lead from it and end either blindly in the subcutaneous fat or in secondary sinuses on the skin of the buttock. Because of this, it has been the

practice to remove a large block of subcutaneous tissue, radical excision, however, makes obliteration of the remaining dead space more difficult than ever. Furthermore, the examination of such a block of tissue shows that the sinuses, as compared with the amount of fat removed, are very small, and thus doubt is cast upon the wisdom of the procedure. It may be argued that, as in the removal of all dermoid or epithelial-lined cysts, it is so essential to remove every trace of epithelium in order to avoid recurrence that the sacrifice of subcutaneous tissue becomes a necessity. More than ten years ago, however, Newell demonstrated that only the original sinus itself is lined with epithelium, the secondary tracks formed by extensions of suppuration from the sinus having a lining of granulation tissue. It is now generally accepted that delay in healing is due not to persistent epithelial lined crypts but to persistent infection in unobliterated portions of the dead space left after excision, and there is much in favour of the more conservative excision advocated by Bartlett, the plane of excision being kept as close to the tracks as possible without opening into them.

This modification of the usual operative technique undoubtedly adds to the difficulty of the earlier stages, but makes it possible to close most of the wounds without tension and to obtain primary healing in two weeks. Although the experienced operator can tell where the sinus tracks are by the appearance of the adjacent tissues, those less familiar with the operation will prefer to inject the sinus with dye as a first step. Injection has been criticized because of the risk of spreading infection thereby, but if the first principle has been satisfied and drainage has been established, the risk is negligible. The injection must be efficiently performed, a solution which will travel readily along the tracks, such as Bonney's or methylene blue in ether, being used. It may be necessary to inject under moderate pressure, preventing back-flow by placing a purse string suture around the orifice of the sinus and tightening it when the needle has been inserted.

Obliteration of the dead space left after excision of the sinus is finally effected only by the natural process of healing, but this may be aided by suturing the wound, provided that this can be done without tension, that infection has been controlled by previous drainage, and that excision has not been performed through the scar tissue of previous unsuccessful operations. In such circumstances the wound must be packed and allowed to heal by granulation.

If suture is to be attempted there are still many questions to be answered. Should buried sutures be used to approximate the deeper layers? The tendency in Great Britain has been to forbid the use of any irremovable sutures or even ligatures which might act as foreign bodies and have to be discharged before healing can take place. Catgut, although 'removable' by the process of its absorption, has been universally condemned in this operation. The answer surely is that, provided the wound is aseptic, a few buried fine silk or linen thread sutures are permissible, ligatures may be avoided by using the diathermy cautery, hot packs and patience. Is drainage good or bad? The risk in drainage, as always, is infection, but free drainage for twenty-four hours through the upper end of the wound does no appreciable harm, and the benefit of avoiding a haematoma is worth the risk. Should skin flaps be fashioned? If there is tension when the gap is being closed, a skin flap is the only alternative to packing the wound open, a closed wound in the middle line is an advantage even at the cost of an unsutured wound in the buttock. If conservative excision as described above can be achieved, the question of flaps should not arise.

Failure to obtain primary healing after excision may be due to postoperative bleeding, to unobliterated dead space, and to infection. Even if the dead space has been successfully dealt with, it must be remembered that the wound edges may be pulled apart by excessive movements of bending or turning the body, and especially by sitting. It is therefore essential that patients should remain completely at rest in bed in the lateral position until healing is well advanced. Infection must be avoided by preliminary drainage of pus from the sinus, by taking care not to cut across any of the tracks during excision, and by frosting the wound with sulphonamide powder, sealing it off from the anus and keeping the bowels confined for several days after operation. Penicillin is unlikely to be useful owing to the prevalence of coliform organisms in the neighbourhood.

An entirely new approach to the treatment of pilonidal sinus is made by Peterson and Ames who deliberately neglect all the principles of treatment accepted hitherto. By their method preliminary drainage becomes unnecessary, the sinus is not excised,

there is no dead space to obliterate, and the patients are returned to duty within a week of operation. Under local anaesthesia the sinus and all its extensions are slit open and the overhanging edge of the skin is trimmed away. A thin wedge-shaped strip of subcutaneous tissue is excised all round between the skin and the lining of the sinus so that these two layers come together easily, and they are held in apposition by a continuous suture of fine non absorbent material such as wire or silk-worm gut. Thus at the end of the operation all that remains of the sinus is an epithelial-lined furrow continuous with the skin of the natal cleft—in the words of the authors the sinus is used as skin “where it belongs”. They have found too, that the skin soon thickens to the proper texture. No recurrences have been reported in three years of continued observation.

The method merits an extended trial, but any surgeon wishing to adopt it should consult the original article for the details of operative technique and after-treatment.

CARCINOMA OF THE PROSTATE

The publicity accorded even in the lay press to the hormone treatment of carcinoma of the prostate does not take any account of the difficulties in diagnosis and of the alternative methods of treatment, which are ably reviewed by Morson. Prostatic fibrosis, with or without calculi, may be mistaken for carcinoma, and the occurrence of a carcinomatous focus in an apparently innocent enlargement of the prostate may be incapable of recognition until the tissue removed at operation is examined histologically. Indeed there are many carcinomatous prostates which indicate their presence by metastatic deposits in the glands of the groin—a puzzling anatomical phenomenon which Morson explains as a spread of disease along the lymphatic vessels which run with the vas deferens.

The biochemist has come to the aid of the surgeon, however, and the estimation of acid phosphatase in the blood is now established as a reliable diagnostic aid except in the very earliest stages of the growth of a prostatic carcinoma. The cells of the normal prostate gland are rich in acid phosphatase; castration causes a diminution of, and subsequent administration of androgen produces an increase of, acid phosphatase in the blood, and thus prostatic activity may be assessed. Many carcinomata of the prostate are sufficiently differentiated to respond “normally” to hormonal stimulation, and to react to androgen by secreting acid phosphatase. The normal blood content of acid phosphatase is up to 2.5 units per 100 cubic centimetres of blood; 5–10 units excites suspicion, and over 10 units is diagnostic of carcinoma (Dodds). It appears that while the growth is still confined within the capsule of the gland the increase in acid phosphatase is small; a significant increase occurs when the growth bursts through the capsule, and the greatest figures are found when metastases are present.

Morson's extensive experience of surgical treatment has shown that suprapubic and perineal “excisions” for carcinoma of the prostate are unjustifiable; that none in whom carcinoma had been established and who had been treated with radium needles inserted from the bladder and the perineum, survived for five years; that castration improves micturition temporarily by causing atrophy of the seminal vesicles and of the residual normal prostate, but does not kill the carcinoma; that obstruction can be relieved by transurethral resection, suprapubic cystotomy and diathermy, or transplantation of the ureters, in that order of preference.

The symptomatic relief obtainable by the far simpler methods of hormone therapy illuminates this gloomy picture with a gleam of hope; time will show whether or not the disease can be completely controlled in this way. Whereas orchidectomy cuts off the chief supply of androgen, oestrogen arrests its output from the testis by inhibiting the supply of gonadotrophin from the pituitary gland. Stilboestrol, although not the most active form of synthetic oestrogen at present available, is the substance of which we have most experience, and may be given by the mouth in doses of 5 milligrams thrice daily as an initial intensive course; later, between 1 and 5 milligrams daily constitute the maintenance dose. Dosage should be regulated according to the amount of acid phosphatase in the blood, which, as explained above, indicates the degree of activity of prostatic cells both normal and neoplastic, and thus provides a measure of the efficacy of the treatment. There are, however, many other less exact evidences of effective treatment: pain is abolished, appetite is restored and

weight is regained, lymphatic deposits and oedema decrease, and even bony metastases have sometimes appeared to regress. It is of interest to note that changes in the alkaline phosphatase in the blood seem to be associated with the presence and the activity of bony metastases.

It has commonly been supposed that castration and stilboestrol have similar effects upon prostatic cellular activity, and that one may be used to reinforce the effect of the other, it has been suggested that castration might be carried out as the first step in treatment, and that if the effect on acid phosphatase is inadequate, stilboestrol should be given to reduce cellular activity to the required degree. Clinical observations by Dean, Woodward and Twombly show that the matter is not quite so simple, they noticed that if recurrences appeared, as they are apt to do, some seven or eight months after castration, oestrogen was ineffective, similarly, castration failed to arrest the growth of recurrences if oestrogen had been the first treatment. The two thus seem to be opposite rather than similar forms of therapy, and this opinion receives support from estimations of the oestrogen, androgen and gonadotrophic hormone in the urine during treatment by one or other of the methods. The authors' final conclusion is that oestrogen therapy is to be preferred, since with it relapses are less frequent than they are after castration.

Stilboestrol has produced such remarkable effects in carcinoma of the prostate that it has seemed to be justifiable to use it in other forms of malignant disease, especially in carcinoma of the breast. The results of an investigation organized by the Section of Radiology of the Royal Society of Medicine (Discussion) are disappointing, the majority of breast carcinomata showing no improvement. The few cases which did respond were patients over the age of 60, the tumours were of the more cellular ill-differentiated type and had not received any previous surgical or radiological treatment.

PATENT DUCTUS ARTERIOSUS

It is seven years since Gross of Boston performed the first successful ligation of a persistently patent ductus arteriosus, and experience which has accumulated since that time has clarified the indications for the operation. Many of those successfully treated have been so desperately ill that the mere chance of achieving something when there was nothing to lose has justified a procedure which may still be rightly regarded as heroic surgery.

Patency of the ductus arteriosus may be the cause of poor general physical development as well as of cardiac fatigue, and either of these effects may call for relief by operation, but the clearest and most urgent indication is subacute bacterial infection with *Streptococcus viridans*. It has been estimated that the incidence of this complication may be as great as 25 per cent, and although future practice may depend upon the effects of penicillin on the infection, at present the best hope lies in surgical treatment. Bearing in mind these serious results of the anatomical defect it is not surprising that after the age of 17 a patent ductus arteriosus should mean a reduction in life expectancy of about 25 years.

Ligation of a patent ductus arteriosus complicated by infection was performed for the first time in Great Britain by Tubbs in 1939, and he has since recorded the details of nine infected cases treated between then and 1943. Six of the patients were well at the time of the report, from fifteen months to over four years after operation. The earlier stages of the operation present no difficulty to anyone familiar with the technique of thoracic surgery, and the ductus can usually be recognized as soon as the mediastinal pleura has been incised just behind the phrenic nerve and below the aortic arch. Occasionally the ductus lies almost entirely within the pericardial sac, when its exposure becomes more difficult.

The stripping of the cellular tissue under the arch of the aorta off the anterior surface of the ductus is conveniently done with a pledget of gauze, but the freeing of the posteromedial surface may be a worrying and even hazardous procedure because it cannot be done under direct vision. Furthermore, in the infected ductus, inflammatory changes are liable to extend through its coats to the exterior, particularly at the pulmonary artery end, and actual aneurysmal dilatation, with additional risk of injury to the thinned-out wall, may be encountered. The close proximity of the left recurrent laryngeal nerve is an additional anxiety. For these reasons it is better to work round the aortic end of the ductus first and then to free it as far towards the

pulmonary artery as possible, so that there may be the maximum distance between ligatures placed close to each end.

The question has been raised of division of the ductus after it has been doubly ligated, but it would appear that the risk of uncontrollable haemorrhage in such a procedure is too great. Moreover, good results have followed ligation alone.

The explanation of the cure of infection after ligation of the ductus has given rise to much speculation, but cannot be regarded as settled. Venous blood is supposed to be inimical to the growth of bacteria and therefore once the stream through the ductus is stopped, the vegetations at the pulmonary end, which had previously been flourishing in the admixture of arterial blood, must die. Bacteriological evidence in support of this theory is lacking; the more popular view is that of Touroff who "supposes that the cessation of the rapid stream through the ductus results in much diminished fragmentation of the infected clot, and that the lung capillaries, now less dilated and fed by an arterial stream no longer raised in pressure or volume, are able to filter off the few emboli which are formed" (Tubbs). Whatever may be the correct explanation, the value of surgery as a life-saving measure cannot be doubted.

REFRIGERATION

The physiological effects of moderate or extreme degrees of cold applied to the body either locally or generally are of great scientific interest and of much practical importance. Exposure of the whole body to moderate cold increases metabolism; severe chilling of a limb, however, brings its metabolic activity almost to a standstill, impairs or abolishes the excitability and conductivity of the nerves and profoundly alters the circulation not only in the minute vessels but also in the arteries. Pathological processes, too, are affected, the activity of new growths and of bacteria being greatly diminished.

In the last few years the use of refrigeration of limbs to induce anaesthesia prior to amputation has been adopted fairly extensively, particularly when operation has to be undertaken for gangrene or for severely mutilated limbs after accidents. In such circumstances there are many factors which combine to render surgery hazardous, and it is worth while studying them in greater detail in order to gauge the extent to which refrigeration may prove to be of value even when anaesthesia is not the primary requirement.

In obliterative arteritis the pain in the extremity (which is worst when the patient is at rest in bed) and finally the onset of gangrene are indications that the metabolic needs in the affected tissues can no longer be supplied by the trickle of blood reaching them. One obvious method of dealing with the situation is to cool the part and thus to diminish local metabolism and bring about a relative improvement in the blood supply. To wrap the limb in cottonwool and apply heat is not merely useless, it is positively harmful; it does not relieve symptoms and precipitates gangrene by increasing local tissue activity. By keeping the ischaemic limb cool and by warming the rest of the body—especially the unaffected extremities—it may be possible to produce reflex vasodilatation in the diseased limb, and thus create an absolute as well as a relative improvement in its blood supply.

Once gangrene is established, bacterial toxins are liable to be added to the other harmful chemical substances which are being absorbed from the dead and dying tissue, and dramatic improvement occurs after the total exclusion of the gangrenous part from the circulation—a condition that can be achieved only if the part is refrigerated. Ice bags are packed around the extremity and between two and four hours later, when the part is anaesthetic, a tourniquet is applied slightly above the gangrenous area but distal to the proposed level of refrigeration and also distal to the proposed level of amputation. Rapid amelioration in the general state ensues with a fall of temperature and of pulse rate, as well as relief of pain and return of appetite; twenty-four or forty-eight hours later amputation can be undertaken with far less risk, especially if shock is minimized by the use of refrigeration anaesthesia (Large and Heinbecker).

Ice bags are applied around the limb in order to cool a ring of skin where a second tourniquet is to be applied, and this can be done painlessly after one and a half hours' exposure to the ice. The level chosen for the second tourniquet should be conveniently removed from the site of amputation; the risk of damaging the tissues distal to the tourniquet is overcome by immediately packing cracked ice around the

whole limb to well above the level of the proximal tourniquet. The distal tourniquet must not be removed. The usual technique of refrigeration anaesthesia is then followed. The head of the bed is tilted up so that the trough made by a mackintosh sheet beneath the limb is inclined slightly away from the patient's body, and as the ice melts the water can drip into a bucket at the foot of the bed. The limb must be completely buried in ice, and fresh blocks must be pushed in behind it from time to time lest it should have only the wet mackintosh sheet on which to rest, with the result that in that region the temperature of the limb might not be kept sufficiently low. After a further interval of two or three hours—depending upon the bulk of the limb—the patient is transferred to the operation theatre and is lifted straight out of the trough of ice on to the table.

The amount of sedative and anodyne drug needed will vary with the patient. Some sedative may be required when the first ice bag is placed around the limb, morphine or one of its equivalents must be given when the amputation tourniquet is put on.

The skin is carefully cleaned because some commercial ice has been found to contain gas forming organisms, and the amputation is carried out in the usual way except that hot swabs are not allowed and every effort must be made to keep the surroundings cool. When the main vessels have been secured the tourniquet is removed and haemostasis is completed. Healing is apparently unaffected by the procedure, and the operative shock is surprisingly slight.

Another indication for excluding the distal part of a limb from the circulation is a severe crushing injury, when shock results from exudation of fluid into the damaged tissues and possibly from absorption of toxic substances as well. The combined application of a tourniquet and of refrigeration is a very great help in maintaining the patient's general condition, and enables the surgeon deliberately to choose the best time at which to operate instead of being forced to carry out a desperate operation in adverse circumstances. This is yet another example of the fact that improvements in technique tend to banish the dramatic from surgery. Actually it is possible to exclude a crushed extremity not only from the circulation, but also even from the surgeon's mind so that he may tackle a more urgent problem first and return to the limb at his convenience. This was the strategy of Mock and Tannehill when faced with a fractured pelvis complicated by gangrene of the leg, others have recorded cases in which visceral injuries such as wounds of the bladder and urethra have been attended to first, and the damaged limb has been maintained in a state of refrigeration until recovery from the first operation was sufficiently advanced to permit of its amputation (Miyakawa).

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OBSTETRICS AND GYNAECOLOGY

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OBSTETRICS

Posterior lobe hypophysis fractions and the intact human uterus

Chassar Moir studied the effect of posterior lobe hypophysis fractions on the intact human uterus by means of a small intra-uterine bag connected by a water-filled tubing to a mercury manometer which recorded the variations of intra-uterine pressure on a moving drum, and his findings are as given below.

The non-pregnant uterus.—The response varies with the time in the menstrual cycle. In the first half (the oestral or pre-ovulation phase) the contractions are irregular and of small magnitude, and come at 30-second intervals. At midcycle, that is after ovulation, there is a gradual change, the waves becoming stronger and more regular as the cycle advances (the luteal phase). There is therefore no ground for supposing that the corpus luteum or corpus luteum extracts such as progestin have a sedative effect on uterine contractions, as had been supposed following the observations of Knaus. Study of the posterior hypophysis fractions separately showed that the contractions are due to the pressor factor (vasopressin, Pitressin) and not at all to the oxytocic principle (oxytocin, Pitocin).

The pregnant uterus.—In Moir's series, in early pregnancy the response to intra-muscular injection of posterior pituitary extract was feeble, but after an operation for evacuation of the uterus its response was much increased and was again more marked to Pitressin than it was to oxytocin. In the later months of pregnancy the contractions before injection of pituitary extract vary considerably from case to case. In some the uterus is relatively inactive; in others considerable activity is present although the contractions are still painless in character. Posterior pituitary extract in a dose of 2 units given intramuscularly causes the contractions to increase in both force and frequency, the effect being greater when spontaneous activity is already in evidence. Both Pitressin and Pitocin are capable of giving rise to this stimulation, but contrary to the findings in early pregnancy Pitocin is now the more powerful. During labour the uterine contractions of the first stage are very similar to those of late pregnancy and the response to undifferentiated pituitary extract is also similar although more pronounced. The uterus responds to both Pitressin and Pitocin, but the response to Pitressin is feeble as compared with the spectacular response to Pitocin.

These experiments clearly show that as pregnancy approaches term the uterus changes in behaviour. Whereas in early pregnancy it reacts to Pitressin, the response to that substance later somewhat declines; conversely the response to Pitocin, previously uncertain, later becomes marked, and as parturition approaches far surpasses the response to Pitressin.

The puerperal uterus.—The uterus after delivery spontaneously contracts at regular and fairly frequent intervals: every two or three minutes. By the end of the first week the contractions come at longer intervals—ten minutes or more—and there are often long periods of relaxation. The response to pituitary extract in the first few days of the puerperium is very similar to that seen in labour. After the first week it becomes less marked and may be difficult to elicit at all after the eighth or ninth day.

Analgesia and anaesthesia in labour

Pethidine hydrochloride, known as Dolantin and Dolantal in Europe and as Demerol in the United States of America, is a synthetic compound introduced by Eisleb and Schaumann in 1939 in a search for an ideal analgesic with an antispasmodic atropine-like action. Batterman in 1943 studied its effect in relieving pain in a variety of

medical and surgical conditions. It does so, apparently, by raising the pain threshold and by relaxing smooth muscle, 100 milligrams of pethidine hydrochloride, administered parenterally, approximating in analgesic potency to $\frac{1}{2}$ grain of morphine. Besides being a potent analgesic pethidine hydrochloride was found to be relatively safe and not liable to cause serious toxic manifestations. Neither did it tend to cause mental depression, constipation or urinary retention. Unlike opiates it could be used for patients with severe anaemia, disease of the liver or kidneys, or bronchial asthma. Intubation studies demonstrated its spasmolytic effect on the human pylorus and intestines.

This analgesic and spasmolytic action, as well as the absence of toxic effects, soon suggested that pethidine hydrochloride might be an improvement on any analgesic hitherto used for relieving the pains of labour, and many studies have now been carried out. Briefly it may be said that it is a fairly effective analgesic giving satisfactory relief from pain in 65–75 per cent of patients when it is given by itself, and is still more effective when it is given in combination with other sedatives such as hyoscine. It does not seem to diminish the strength or frequency of the uterine contractions or to increase the forceps delivery rate, and several observers claim that it diminishes spasm of the cervix and thus helps dilatation. Unlike morphine it is not a respiratory depressant, and so has little, if any, tendency to cause apnoea of the newly born infant (Cripps, Hall, and Haultain). Gallen and Prescott, however, evidently fearing some slight depressant action, advise that it should not be used in the period of $2\frac{1}{2}$ hours immediately preceding delivery. This has not been confirmed by our experience at University College Hospital, where it is given as a routine measure before Caesarean section under epidural anaesthesia, without any apparent ill effect on the child. Almost its only drawback is that it does not cause amnesia, and so to get this effect it is often used in combination with scopolamine (hyoscine) or barbiturates. By the mouth the action of pethidine hydrochloride is slow and uncertain and it is therefore usually administered by intramuscular injection. The following dosage is generally satisfactory. The first dose of 100 milligrams is given when the os admits two fingers and when regular contractions are occurring. The same dose may be repeated in $\frac{1}{2}$ –1 hour. After injection, pain is relieved in $\frac{1}{2}$ hour and the analgesic effect is maintained for 3–4 hours. A third and fourth dose, each of the same amount, may be given if and when required—usually at 2-hour intervals. To obtain amnesia, scopolamine, $\frac{1}{120}$ grain, may be given subcutaneously at the same time as the first or second injection of pethidine hydrochloride and $\frac{1}{160}$ grain every hour until delivery. Gilbert and Dixon with the third or fourth dose of pethidine give Seconal (sodium propylmethylcarbonylallylbarbiturate), $\frac{1}{4}$ grains by the mouth, and $\frac{1}{2}$ –1 hour later, $1\frac{1}{2}$ grains. Gallen and Prescott combine the pethidine with a stock mixture containing chloral hydrate, 30 grains, potassium bromide, 30 grains, tincture of opium, 10 minims, chloroform water to 1 fluid ounce. They limit the total amount of pethidine given to 400 milligrams in 24 hours, but Gilbert and Dixon sometimes give as much as 650 milligrams.

Continuous caudal anaesthesia—This method of anaesthesia was introduced by Lemmon in 1940 and was first applied to obstetrics by Edwards and Hingson in 1942. The injection is given through the sacral hiatus into the epidural space in the sacral canal. This canal, which is a continuation of the vertebral canal, ends caudally in the sacral hiatus which is formed by the defective fusion of the last sacral laminae and is roofed over by the sacro-coccygeal membrane. The hiatus varies in size but in most cases can be felt as a triangular depression, the apex of which is formed by the spinous process of the fourth sacral vertebra and the sides by the cornua of the fifth sacral vertebra. At this point the epidural space is occupied by blood vessels, by fatty and areolar tissue and by the sacral and lumbar nerves. The dural sac usually ends at the level of the second sacral vertebra so that there is ample room for insertion of a large needle through the hiatus without much danger of penetrating the dura and thus inducing spinal anaesthesia.

Two methods of inducing continuous caudal anaesthesia are in use. In the earlier method an indwelling needle is used, in the more recent method an indwelling urethral catheter is introduced through a 15 gauge spinal needle which is then withdrawn leaving the catheter *in situ*. For the latter method the advantages claimed are, first, that there is less liability to trauma of the vessels and nerves in the canal owing to the use of a flexible catheter which will not tear them, secondly, that the patient

is more comfortable and can lie on her back, whereas with the indwelling needle she must lie on her side throughout labour; thirdly, that the chances of infection are less, since the catheter can be sealed in place with waterproof tape. Through the indwelling needle or catheter, repeated injections of the selected solution can be made, or a continuous drip can be used by means of a gravity apparatus. Siever, who has used this method extensively and reported the results of its use in 1,200 personal cases of labour, employs procaine hydrochloride, 1.5 per cent solution in isotonic saline. Other solutions in use are Metycaine, 1.5 per cent, and amethocaine hydrochloride (Decicain, Pontocaine hydrochloride), 0.25 per cent, both in isotonic saline. The largest amount of procaine hydrochloride used by Siever was 1,000 cubic centimetres of 1.5 per cent solution, and the smallest, 30 cubic centimetres. In addition to thorough disinfection of the skin in the injection area and strict attention to asepsis, two major procedures are necessary to find out whether or not a vein or the dural sac has been punctured. (1) After insertion of the needle and attachment of the syringe, the plunger is withdrawn somewhat in order to aspirate blood or spinal fluid as the case may be. (2) As an additional precaution a test dose of 8 cubic centimetres of the solution is then injected, after which the operator should wait for 10 minutes to see whether a spinal anaesthesia has been given or not. If this is so, or if blood or spinal fluid has been aspirated, the procedure should be abandoned.

The anaesthetic should be begun only after labour is definitely established and the patient is in need of relief from pain. It is contra-indicated in cases of disproportion between the head and the pelvis and in primiparae in whom the head is not engaged at the beginning of labour. Siever recommends that anaesthesia should not be started until the os is 6 or 7 centimetres dilated and the head is engaged. If the anaesthesia is begun earlier, dilatation is slowed and the head fails to descend into the pelvis. If the patient demands relief before this she should be given either a barbiturate or morphine and scopolamine or a barbiturate and morphine and scopolamine.

As to the results, Siever obtained a satisfactory anaesthesia in 94 per cent of his 1,200 cases. The remaining 6 per cent required supplemental anaesthesia for the various reasons given below; it is instructive to consider these in detail since they indicate some of the difficulties likely to be encountered even when the procedure is in the most skilled and experienced hands.

- (1) The needle was inserted into the subarachnoid space.
- (2) Hysterical patients became unmanageable.
- (3) Disproportion of head and pelvis with prolonged labour necessitated discontinuance of the caudal anaesthetic.
- (4) Insertion of the needle into the canal was technically impossible in four cases.
- (5) A psychotic patient who was completely disorientated could not be managed.
- (6) The catheter slipped out in two cases in which the technique of taping was faulty.
- (7) There was severe nausea and vomiting.
- (8) Frank blood was obtained on insertion of the needle.
- (9) There were severe radicular pains.

All observers are agreed that the second stage of labour is greatly altered. As the perineum is anaesthetized the patient has no desire to bear down or to use her abdominal muscles. At the same time the pelvic floor is greatly relaxed so that forward rotation of the occiput is interfered with and persistent occipitoposterior positions and deep transverse arrest of the head are unduly common. The forceps rate is very high and often the head is arrested not at the outlet but in midpelvis, so that forceps delivery may be difficult. Fitzgerald and his colleagues found that the incidence of forceps delivery was increased to 70 per cent as compared with 12 per cent before caudal anaesthesia was used. Siever found the incidence of persistent occipitoposterior cases to be increased to 12 per cent as compared with a previous incidence of 4 per cent. It is claimed, however, that the marked relaxation of the pelvic floor and perineum makes manipulation of all kinds, including forceps delivery, exceedingly easy. In Siever's series there were 38 breech deliveries. Progress in all these was normal, and delivery of the head was easy.

If, therefore, prolongation of the second stage of labour and the increase in the forceps rate and the incidence of persistent posterior positions were the only disadvantages, a good case might be made out for the wider use of continuous caudal anaesthesia in obstetrics. There are, however, other serious risks to mother and child. Siever, one of the chief and most experienced advocates of the method, states that with procaine hydrochloride slowing of the fetal heart occurred after injection

in 1 per cent of his cases. With Metycaine it occurred in 20 per cent. One fetus died *in utero* five minutes after the third injection, within two minutes after injection the fetal heart sounds began to slow and weaken, and gradually stopped. One death from infection at the site of injection has been reported by Hingson and Edwards. In one case of Siever's arachnoiditis developed. Laminectomy was performed and the patient is "gradually recovering bladder function and the use of her legs, but the prognosis is guarded." These dangers were well brought out in a discussion on obstetrical analgesia at a meeting of the Chicago Gynaecological Society in 1943. In that discussion Baptista emphasized the risk of respiratory failure and sudden death involved in the use of intradural injection, stating that this may occur in the most experienced hands and that sudden death may also occur apart from intradural injection. "Caudal anesthesia is no safer today than it ever was," he remarked. "The present practice of using an indwelling needle or catheter in the sacral canal between injections has done nothing but increase the hazards. Although the ever present danger of vascular collapse probably remains the same, the risk of accidental dural penetration is increased. The hazards of needle breakage and infection have been added. The use of such a hazardous procedure *electively* to relieve the usually innocuous pains of labour is unjustifiable. Since the recent advent of continuous caudal analgesia four women have lost their lives because of the procedure *per se*. There have been other 'close calls' reported. Never before has the human nervous system been subjected to the action of such prolonged concentrated anesthesia. The absence of residuals and sequelae remains to be proved." Huber mentioned two cases of his in which Metycaine was given for Caesarean section. After 30 cubic centimetres of a 1.5 per cent solution had been injected vasomotor collapse occurred. The blood pressure fell to 60/40 and so remained for three-quarters of an hour. The fetal heart sounds fell to 60. The baby after delivery was not normal. At the age of seven months it was very markedly abnormal. In another case of Caesarean section the patient also collapsed. The fetal heart sounds fell to 50 or 60 and remained so for a quarter of an hour. After delivery the infant made one or two respirations and then could not be resuscitated.

Most users of continuous caudal anaesthesia attempt to minimize the danger of circulatory collapse by adding a vasoconstrictor such as ephedrine to the anaesthetic solution. Its vasoconstrictor action delays absorption.

It is evident, therefore, that continuous caudal anaesthesia is, even when all known precautions are taken, attended by a certain risk. It should be used only by those who are trained in the technique and who are prepared to give almost continuous attention during its use (Mengert).

Terminal caudal anaesthesia—In this method a single injection is given when the head is just visible at the introitus. Cron and Klieger report on its use in 800 cases, in 88.8 per cent of which completely successful anaesthesia was obtained, whereas in 11.2 per cent there was either partial or total failure. Metycaine, 40 cubic centimetres of a 2 per cent solution, was used and the average duration of the anaesthesia was 89 minutes. With the exception of a temporary fall in systolic arterial pressure of 20 to 30 millimetres of mercury, the total number of side reactions did not exceed 4 per cent. These consisted of transient disorientation, nausea, vomiting, blurring of vision and convulsions—only six of which were prolonged to one or two minutes and they responded quickly to administration of carbon dioxide oxygen mixture and ephedrine. Post partum haemorrhage was minimal. Although the authors do not say so, or give any figures regarding the incidence of forceps deliveries, it is surmised that the anaesthetic was in all cases given to allow immediate instrumental delivery.

The rapid treatment of early syphilis in pregnancy

Two major difficulties are commonly encountered in the treatment of syphilis in pregnant women. One is that patients often come for the first time when they are far advanced in pregnancy, the other, that they fail to attend regularly or cease attendance before completion of the prolonged course necessary when weekly treatments are given. These difficulties have been largely surmounted by the recently introduced intensive therapy. After much experimentation with varying methods and materials, Speiser and his colleagues finally decided that the maximum dose of Mapharsen should be 1 milligram per kilogram of body weight, and that only

one injection should be given daily. The average patient would then get 10 daily injections of approximately 0.06 gramme of Mapharsen. To reinforce this, four artificial pyrexial attacks induced by typhoid vaccine were given on the second, fourth, sixth and eighth days. The first spell of fever was induced by an initial injection of 0.1 cubic centimetre of triple typhoid vaccine given intravenously, the second by 0.2, the third by 0.4 and the last by 0.6 cubic centimetre. Two or three hours after the first injection a second dose of equal amount was administered. In general a fever of 104° F. lasting for about four hours was obtained. Recently bismuth was added to the schedule of treatment, 0.1 gramme of bismuth salicylate in oil being given on the first, third, seventh and tenth days of therapy. Accordingly the standard treatment became established as stated in the table below.

TREATMENT	DAYS									
	1	2	3	4	5	6	7	8	9	10
Mapharsen, 1 milligram per kilogram — —	×	×	×	×	×	×	×	×	×	×
Bismuth salicylate in oil, 100 milligrams — —	×		×				×			×
Typhoid vaccine in cubic centimetres — —	0.1 0.1			0.2 0.2		0.4 0.4		0.6 0.6		

Contra-indications to treatment are active tuberculosis, nephritis, decompensated heart disease, toxæmia of pregnancy, or any chronic hepatic disease.

The results are compared by Speiser and his colleagues with those of routine treatment. Forty-three pregnant patients were treated with massive therapy. There was one death from arsenical encephalopathy. Of the thirty patients who completed the treatment and were kept under observation, good results, that is babies free from congenital syphilis, were obtained in a minimum of 76.6 per cent. If the babies not proved to be syphilitic were eliminated from the calculation the good results would be 85 per cent. Of thirty-four pregnant women treated by routine therapy one died from arsenical encephalopathy and only 50 per cent of the offspring were free from syphilis. So far as this small series is concerned intensive therapy was therefore more effective than was the more prolonged routine.

Penicillin in venereal disease

Penicillin is a substance produced by a mould, *Penicillium notatum*; in its final form it is a yellow powder. It has a very selective action in inhibiting the growth of some bacteria whereas on others it is without effect. The more sensitive are staphylococci, streptococci, pneumococci, gonococcus, meningococcus and *Corynebacterium diphtheriae*; *Escherichia coli* and many others are not sensitive. Unlike most other chemicals it has no harmful effects on leucocytes and yet to certain bacteria it is twice as lethal as is phenol (Fleming). Either the sodium salt or the calcium salt may be used. It is inert when given by the mouth and so either must be applied locally or must be injected intravenously, intramuscularly or subcutaneously. Absorption from intramuscular or subcutaneous injection is very rapid and when it is injected intravenously it disappears quickly from the blood. In order, therefore, to keep up a constant level in the blood, continuous drip is necessary.

Penicillin in prevention and treatment of congenital syphilis.—Lentz and his colleagues report on the treatment of 14 pregnant women with early syphilis, and 8 infants with congenital syphilis. Each of the women gave birth to an apparently normal child at term, except one who was premature but otherwise healthy. Dark-ground examination of the umbilical vein was negative in 5 and was not made in 2. Skiagrams made of the long bones in 4 cases at birth and repeated at six weeks or later were normal in every instance. Three of the infants had positive cord and neonatal blood tests but in each the reaction had fallen sharply postnatally and the test had become normal in less than one month. (It may be necessary to remind the reader that a positive Wassermann reaction in the cord blood may be due to antibodies from the mother and does not necessarily mean that the child has congenital syphilis. When congenital syphilis is absent the reaction gradually gets weaker and by the third month is usually negative.) All the other infants have remained seronegative.

In the period of observation only 3 of the mothers have become seronegative. None had treatment before mid pregnancy.

With two exceptions every pregnant woman so far delivered was given a total dosage of 1,200,000 Oxford units of sodium penicillin, one of those remaining had 2,400,000 units and one failed to complete treatment. Three patients still undelivered had 2,400,000 units each. The injections were given intramuscularly every 4 hours round the clock for approximately 8 days. Infective surface lesions cleared up rapidly and the *Treponema pallidum*, as determined by dark-ground examination, disappeared in less than 8 hours. In no case did dark-ground examination show spirochaetes later than 24 hours after penicillin treatment had been begun.

Infantile congenital syphilis—Nine patients were treated with sodium penicillin but only 3 had so far been under observation long enough to be worth reporting. Two deaths among the 8, possibly not due to penicillin, are also included. Three infants observed for 99, 97 and 79 days, respectively, all became clinically normal. Two infants who showed definite x-ray changes in long bones (syphilitic osteochondritis and periostitis) have resumed approximately normal bone development.

In 6 of the 9 patients the total dosage of sodium penicillin given every four hours round the clock for 8 days was between 16,000 and 19,000 units per pound of body weight. The remaining 3 infants received 2,935, 10,631 and 11,111 units per pound of body weight. In only one of the infants has there yet developed, after a period of 99 days, a completely negative blood serologic reaction. In the other 2, kept under observation for a sufficiently long period, it fell to a comparatively low level. The authors consider that the number of cases is too small and the subsequent history too brief to allow sweeping conclusions to be drawn, but they hold that a total dosage of 2,400,000 units is safe in the pregnant woman and is advisable for the purpose of curing the mother and protecting the child, and that penicillin will eventually replace arsenicals in the treatment of syphilis.

GYNAECOLOGY

Prevention of cancer of the cervix uteri

It has long been believed that one of the chief predisposing causes of cancer of the cervix is trauma in childbirth and superimposed infection (cervicitis) and cervical erosion, and that prevention or cure of erosion would do much to diminish the incidence of cancer. Further proof of this has been provided by Cashman, who has followed up 4,487 patients with chronic cervicitis in whom deep cauterization was carried out. The results, modified from Cashman and statistically analysed, show a reduction of cancer of the cervix of approximately 80–85 per cent.

CAUSE OF DEATH	NUMBER OF DEATHS	
	OBSERVED	EXPECTED
All causes —	156	297.3
All cancers —	26	44.9
Cancer of fundus uteri —	1	2.0
Cancer of cervix —	1	11.6
Cancer of breast —	11	8.3

The table shows that only deaths from cancer of the cervix have been significantly less than expected. The author believes that cancer of the cervix rarely, if ever, develops from normal squamous epithelium but that it develops at the junction of the squamous epithelium and the chronic inflammatory area in cervicitis, either on the surface of the portio or in metaplasia in the glands, and that if cervicitis is eliminated cancer of the cervix will be practically eliminated also.

Pain threshold in dysmenorrhoea

Haman has attempted to settle the question whether patients with spasmodic (primary, intrinsic) dysmenorrhoea actually receive more intense pain stimuli or are merely more sensitive to pain than are normal persons. A sensimeter was used which registered pressure stimuli on the thumb, that is the amount of pressure required to make the subject draw away or wince. The procedure was repeated on the other

thumb and the mean of the two values represented the person's pain sensitivity. The average pain threshold of 100 dysmenorrhoea patients, 50 of whom had primary and 50 secondary dysmenorrhoea, was compared with that of 100 women who had no dysmenorrhoea, 100 women past the menopause, and 100 males. The dysmenorrhoea group had a lower pain threshold than any of the other three groups tested, that is 12.2 as compared with 14.9 for young healthy women, 15.2 for postmenopausal women and 14.6 for males. Patients with the primary type of dysmenorrhoea showed the highest rate of sensitivity of any group or sub-group in the entire series—a threshold of 11.4 as compared with 12.9 in the secondary type of dysmenorrhoea. The lowest rate of sensitivity (15.2) was recorded among the postmenopausal women. These again were divided into two groups: those who had suffered from intrinsic dysmenorrhoea during menstrual life, and those who had not. The former had a distinctly lower pain threshold than had the latter. The author concludes that in women with dysmenorrhoea there is an intrinsic factor which makes them more susceptible to pain than are normal persons.

It would be of interest to carry out the test on a group of girls before puberty in order to find whether or not dysmenorrhoea develops only in those with a low pain threshold. It could then be concluded that the low pain threshold was a factor in the causation of the dysmenorrhoea and not its result.

Penicillin in sulphonamide-resistant gonorrhoea in women

Greenblatt and Street state that the early reports of an 85 per cent cure rate in gonorrhoea by treatment with sulphonamides can no longer be sustained, since persistence of certain strains which have permeated a selected stratum of the population has reduced effectiveness of these drugs to little better than 55 per cent. Moreover, improved bacteriological technique has helped to uncover many carriers of the gonococcus in whom all clinical signs and symptoms were absent. Greenblatt and Street consider that penicillin is many times more efficient as a bacteriostatic and bactericidal agent than are the sulphonamides and that it is especially useful in eradicating sulphonamide-resistant strains of the gonococcus.

One hundred and nine patients were treated with penicillin, of whom 93 per cent had had one or more courses of sulphonamides without success. After the use of penicillin cultures became negative within 12–24 hours. Patients in whom a positive smear or culture was obtained later than the fifth day after administration of penicillin had been begun were classed as failures; there were 11 such patients. The total amount advised is 150,000 units given intramuscularly in doses of 10,000–20,000 units at 3-hour intervals round the clock—usually about 8 doses. Harford and his co-workers record the results of treatment of 12 families with sulphonamide-resistant gonorrhoea who were cured with penicillin. Before the penicillin therapy each had had intensive sulphadiazine therapy. In all but 2 cases a total dosage of 75,000 units or less was employed. All but one of the 12 were observed in hospital for a period of 30 days after treatment. In this time only one questionable relapse was noted. One of the patients was a woman, aged 20 years, with gonorrhoeal urethritis and cervicitis, who failed to respond to 3 courses of sulphadiazine. The concentration of the drug in the blood reached 12–14 milligrams per 100 cubic centimetres. Shortly after the third course gonococcal peritonitis developed which responded promptly to administration of 60,000 units of penicillin given over an 8-hour period, that is 20,000 units given intravenously, and then two intramuscular injections of 20,000 units each at 4-hour intervals. Observation for 30 days afterwards did not reveal any recurrence.

Gonococcal vulvovaginitis in children

Compton and his colleagues state that a specimen of pus from high in the vagina examined by direct smear is sufficient for diagnosis. No child should be treated unless she is accompanied by an adult to whom instructions can be given regarding prevention of spread of infection, and unless an attempt is made to find the source of infection. Treatment can be carried out in the out-patient department. Whereas good results can be obtained with sulphonamides the authors believe oestrogens to be the remedy of choice since there is a risk of sensitizing the child to sulphonamides—and these should be reserved for the most lethal diseases of childhood, or for

gonorrhoea in which there are complications or when oestrogens fail. The dosage was as follows. The synthetic preparation stilboestrol was given in doses of 0.5 milligram daily between the ages of 6 months and one year, and 1–3 milligrams daily between one and 10 years. Hexoestrol was given in four times that amount. Natural oestrogens in the form of Amniotin perles, oestriol gelatin capsules or oral oestrogenic tablets were all administered as vaginal suppositories. The oestrogens cause cornification of the vagina and the average total dosage until complete cornification was obtained was approximately 35,000 international units. The child is examined at weekly intervals until there are three successive negative smears and thereafter at monthly intervals until smears have been negative for 3 months and then at intervals of 3 months, the patient is discharged when she has been well for one year. Three hundred and eighteen cases of gonorrhoeal vulvovaginitis were diagnosed. One hundred and fifty three were observed for one year after the smears had become negative. Of these 153, 122 were treated with oral or vaginal suppository oestrogens, natural or synthetic, 12 with sulphathiazole or sulphadiazine, and 10 by a combination of oestrogens and sulphonamides. All three methods were found to be effective in causing cornification of epithelium, development of a hydrogen ion concentration of 4.5–5.5 and a negative smear for gonococci. As a precaution the drug was continued for one week after the smear had become negative.

Treatment of amenorrhoea

The rational treatment of amenorrhoea due to deficiency of the follicle stimulating and luteinizing hormone of the anterior lobe of the hypophysis cerebri or to ovarian deficiency, should be by means of gonadotrophic hormones derived from the anterior lobe of the hypophysis itself. These, however, are not available in sufficient quantities. The chorionic gonadotrophin obtained from pregnancy urine (anterior pituitary like substance, A.P.L.) does not act on the human ovary. The same is true of the gonadotrophic hormones obtained from the serum of the pregnant mare. When, however, small quantities of anterior pituitary extract are combined with chorionic gonadotrophin, a synergistic effect is obtained which far surpasses the effect produced by either of these hormones separately. Within recent years this synergistic compound has been produced commercially under the name, synapoidin.

Davis has used this substance in twenty seven cases of amenorrhoea which for clinical purposes he classified according to the organ the failure of which was presumed to be primarily responsible, whether that was the hypophysis, the ovary, the uterus, the thyroid gland or the adrenal gland. The cases due to primary functional hypophyseal deficiency present signs and symptoms similar to those of Fröhlich's syndrome, namely adiposity and genital hypoplasia, the excess fat being characteristically deposited in the lower abdomen, the thighs and the breasts. The basal metabolic rate is low. The uterus is small with scanty endometrium and in the ovaries there is delay or absence of follicle maturation. Amenorrhoea due to primary deficiencies of ovaries, uterus, thyroid gland or adrenal gland is rarer. In the last there are apt to be masculinizing symptoms in addition to the amenorrhoea. Treatment was not begun until the precise cause of the amenorrhoea had been determined as nearly as possible. The investigation included a careful examination for the purpose of excluding gross abnormalities, x-ray examination of the hypophyseal fossa, (iodized oil) hystero-graphy. In 19 of the 27 patients the amenorrhoea was of primary hypophyseal origin, in 6 it was the result of ovarian destruction (by x-rays or radium, tubercle, chronic inflammatory disease and so forth) and in 2 the thyroid gland was at fault. The dose of synapoidin used was 1 cubic centimetre, given intramuscularly 3 times weekly for 3 weeks, provided haemorrhage did not occur or the ovaries enlarge unduly. Gross enlargement of the ovaries occurred in 6 cases during the treatment and it took about 6 weeks for them to return to normal size. When undue enlargement or haemorrhage occurs treatment should be stopped. Careful supervision is therefore necessary during treatment, and the patient should be examined frequently so as to discover ovarian hypertrophy without too much delay.

As to results, of the 27 cases an apparently permanent cure, that is restoration of normal menstrual rhythm for at least six months, was obtained in 14, there was temporary improvement in 6 and no improvement in the remaining 7. The type of patient found most likely to benefit was one with a mild Fröhlich's syndrome, especi-

ally when increase in weight was fairly marked. The duration of the previous amenorrhoea did not seem to influence the results.

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CANCER

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The term, cancer, dates from the mythological period of medical history and has no aetiological significance other than that which it has acquired by centuries of popular use. The fashion of restricting the term, cancer, to carcinoma, to the exclusion of sarcoma, seems to be quite unjustifiable, since we know from experimental work that many carcinogens can induce either type of tumour. In this article "cancer" will be used in the broadest sense to cover malignancy of any part of the body and of any species of animal. Progress in our knowledge of cancer has been so great, particularly since the early nineteen thirties, that it is impossible to do justice to all the original work in a short article. In order to avoid presenting a mere catalogue of facts, of which some might appear to have little bearing on one another, various aspects of the problem are presented under main headings, prominence being given to those achievements that seem to me to have fundamental importance. In the final section an attempt is made to survey the present state of our knowledge. For the reader who wishes to make further study of any aspect of cancer, references are appended consisting mainly of critical reviews, each with an extensive bibliography of original papers.

DIAGNOSIS

The possibility of detecting cancer in a treatable stage depends first on the alertness of the patient and secondly on the clinician who first examines him. A slowly rising public consciousness in this matter is making a small contribution to early diagnosis, but still leaves much to be desired.

Non-specific methods

Routine examination of large groups of people, such as occurs during wartime, has been responsible for the detection of some early cancers. For example, mass radiography of the chest for the detection of early tuberculosis has revealed a few unsuspected intrathoracic tumours. The use by experts of new or improved instruments—such as the flexible gastroscope introduced by Schindler—has increased the accuracy of early diagnosis of cancer in certain regions of the body.

Specific tests

Many and varied attempts at the serodiagnosis of cancer in general have given disappointing results. Those reactions which give a significant proportion of correct diagnoses seem to depend upon cachectic changes of a non-specific nature in the body. The subject was recently reviewed by Maver. The available evidence is against the conception of cancer being a specific disease in the sense that tuberculosis, or malaria, is specific. If this view is correct it is not surprising that specific tests for cancer have not been found. More encouraging results have been obtained in certain types of cancer involving organs that normally produce internal or external secretions which can be estimated. For instance, the Gutmans' estimation in 1936 of serum acid phosphatase in patients with osteoplastic or osteolytic metastases, drew attention to the association between carcinoma of the prostate and a rise in serum acid phosphatase. In the presence of bony metastases there is also a rise in the serum alkaline phosphatase. These reactions are of diagnostic and prognostic significance. Another example of this kind is the detection in a high percentage of cases of prolan A in the urine of patients with teratoma testis. Such specific tests can be developed only for cancers which upset the normal balance of recognizable secretions or metabolites.

TREATMENT

Surgery and various types of radiation remain the principal methods for the radical extirpation of most forms of cancer. It is difficult to imagine much further advance along surgical lines, but the technique of pulmonary lobectomy is one branch of surgical achievement which has converted the hopeless prognosis of pulmonary cancer into one that gives some prospects of cure in early cases. Despite the great improvements in the design of radiological apparatus and improved calculations of dosage charts, there has been in recent years no striking improvement in the results of radiological treatment, nor has it been possible to extend such treatment to some of the commoner forms of cancer, for example cancer of the stomach. Improvements have rather been attributable to earlier or more thorough irradiation of tumours already known to respond favourably to radiotherapy. Unfortunately, the radio-sensitivity of tumour is not an indication of its curability, and some very radio-sensitive tumours, for instance lymphosarcoma, usually recur rapidly and kill the patient in spite of treatment.

A new development of radiological treatment was introduced by Lawrence, who injected artificially radio-active phosphorus (P^{32}). This element has a half-value period of 14.3 days, and emits β rays capable of penetrating 2-4 millimetres of tissue. Its distribution in the body is the same as that of normal phosphorus, and its action is therefore concentrated in sites where this element is present in the greatest amount. Chronic lymphatic and myelogenous leukaemia, and osteogenic sarcoma, respond favourably to P^{32} . The nature of the response seems to be essentially the same as that excited by the conventional forms of radiotherapy; but the distribution of the dose is completely different and is theoretically more satisfactory, since it is selectively distributed throughout the body. Other radio-active isotopes that would have a different distribution and might therefore be suitable for the treatment of other types of tumour, will no doubt be prepared and tested. The essentials would be the demonstration of selective absorption by the tumour tissue for the isotope to such an extent that an effective roentgen equivalent dose could be administered.

Hormonal treatment

The recent demonstration that prostatic cancer can be controlled at least partially by administration of oestrogenic hormones has developed from the work of Huggins who showed that castration exercised a beneficial effect on the development of this type of cancer. The injection of synthetic or natural oestrogens, with or without castration, exercises a similar control. Reduction in the size of the tumour and prolongation of life have been obtained by several independent investigators, but it is not certain that the disease can be cured by this method of treatment. In fact, biopsy material from a clinically satisfactory case may show apparently viable tumour cells alongside other malignant cells in various stages of degeneration. This in no way detracts from the great value of the method. Treatment of cancer of the breast with stilboestrol and other synthetic oestrogens seems to be widely employed at the present time—although the basis for the treatment is by no means clear—and it should be borne in mind that the administration of oestrogens to mice has proved to be an efficient method of inducing mammary cancer. Nevertheless some measure of improvement in a minority of cases treated in this way was recently reported by Haddow and others.

Chemotherapy

Attempts to control human cancer by chemotherapy have been disappointing, but Haddow's demonstration in 1935 of tumour-inhibiting properties in some carcinogenic hydrocarbons has led to the synthesis of many new substances, some of which retain the inhibiting property without being carcinogenic. This promising work is still in the experimental stage.

PROPHYLAXIS

Prophylaxis against cancer is at present limited to the prevention of industrial types of disease in which carcinogenic agents are a recognized risk. Cancer of the skin in pitch workers, of the bladder in aniline workers, of the long bones in radium workers, are examples. Suitable protective measures can prevent the occurrence of these types of cancer. Nevertheless cancer of the scrotum is still enormously more common in

chimney-sweeps than it is in the rest of the community, as was recently shown by the Kennaways. There are good reasons for supposing that some of the commonest forms of human cancer, for example cancer of the stomach, are also due to extrinsic causes which if recognized might be eliminated.

STATISTICAL RESEARCH

Prospects for improving both preventive and active treatment of human cancer depend largely upon accurate statistics which may often form the basis of experimental research. These methods have already led to the recognition and preventive treatment of several forms of industrial cancer. The rarity of gastric cancer in animals and its great prevalence among human beings point to the influence of extrinsic factors, of a controllable nature, which might be elicited by suitable statistical enquiry. Two Conferences on gastric cancer were held in America in 1940 and 1944, at which the urgency of tackling the problem was stressed. Between a quarter and a half of the number of all cancer deaths in European and in North American populations are due to cancer of the stomach. In the United States of America conditions vary greatly, but taking the large cities as offering the best available facilities, the prospects of improving the results of treatment by radical gastrectomy depend mainly upon earlier diagnosis. Oughterson gave the surgical responsibility, that is cases accepted for radical resection, in New Haven, between 1931 and 1938, as only 10.7 per cent of all cases seen, nevertheless a fifth of this small group survived radical operation for five years.

In the case of human habits, those that are developed voluntarily and pleasurably are less open to statistical analysis than are those associated with industry. There is no dispute about the causal association between soot and chimney-sweep's cancer of the scrotum. On the other hand, betel nut chewing by the natives of India and Ceylon is generally accepted in Great Britain as being a cause of cancer of the mouth in these people, but tobacco smoking, as being a possible cause of the same type of cancer, is not generally accepted. Yet, the destructive distillation of many organic substances, including tobacco, yields demonstrable chemical carcinogens, whereas no recognized carcinogen has so far been demonstrated in betel-nuts. A statistical study based on the same criteria as would be employed in assessing industrial risks would give a scientific answer to problems such as the foregoing, and it is to be hoped that such studies will form part of any projected scheme for cancer control on a national scale.

EXPERIMENTAL RESEARCH

Genetics and cancer

Early in the present century breeding experiments were undertaken by many workers to see whether tumour bearing animals could or could not transmit the disease to their progeny. As a result of inbreeding, chiefly in mice, certain strains were developed that showed either great or little tendency to cancer of some part of the body. Since mammary cancer in mice has been more extensively studied than have most other types, it is discussed shortly in this and in succeeding sections. By line breeding (brother to sister matings) "pure" strains of mice have been developed in which the incidence of mammary cancer in the females can be predicted with some accuracy. Two strains may be considered as typical: (1) strain A, with approximately 90 per cent incidence and (2) strain B (C 57 black), with a negligible incidence. Many similar strains have been developed and the history of these and of other aspects of genetics in relation to cancer have been recently reviewed by Blank. Those interested in this fundamental form of research should read his article, which does not lend itself to further condensation. One of his conclusions, however, may be quoted: "Cancer is not a unit of disease, at least so far as its genetic behavior is concerned. Tumours of different sites and types differ in their genetic behavior."

Extrachromosomal factors

Much controversy and many experiments resulted from the establishment of high and low cancer strains in mice. New light was thrown on the subject in a report by Little on the work of the staff of the Roscoe B. Jackson Laboratory. They showed that when high mammary cancer strain females (A ♀), were mated with low mammary

cancer strain males (B ♂) the resulting female hybrids (ABF 1) had a high rate of incidence of mammary cancer, but that genetically similar hybrids (BAF 1) from B females and A males had a low rate of incidence. Since there is no theoretical difference between the chromosome patterns of ABF 1 and BAF 1, some other or "extrachromosomal" factor had to be postulated in order to explain the facts. (The term, extrachromosomal, although widely used, is ambiguous. What is meant is a factor carried in the cell but not by the chromosomes.) The most obvious possibility was that breast cancer was transmitted to the offspring by something in the mother's milk. In a series of brilliant investigations, Bittner has established beyond doubt that a factor in the mother's milk is responsible for transmitting mammary cancer to females, not only of the same strain but, by foster nursing, to other strains. Conversely, female offspring of strain A may be protected against the risk of mammary cancer if they are nursed throughout by foster-mothers of strain B. The milk factor has also been transmitted experimentally by extracts of tumour or of spleen from high cancer strain mice to females of low cancer strains. The extrachromosomal factor is thus, in a limited sense, infective and is often referred to as a virus. Other types of cancer, for example cancer of the lung, have also been studied in the foregoing and other strains and no extrachromosomal factor has been demonstrated to account for their transmission. It is obvious therefore that generalizations about the hereditary nature of cancer are unjustifiable, even in artificial inbred lines of animals. Hereditary factors, however, must play some part in determining the susceptibility of individuals to cancer, as to other diseases, as is clearly shown, for instance, in the rare disease xeroderma pigmentosa, in which hereditary skin lesions become malignant after exposure to light.

Infective agents (viruses)

The term, virus, is generally held to mean an ultramicroscopic living organism, but at present a number of plant diseases are known to be transmissible by crystallizable proteins, and these are also termed viruses. Provided, therefore, that no precise definition of the living or non-living nature of viruses is implied, the term can conveniently be used for any ultramicroscopic infective pathogen. The first suggestion that a neoplastic disease could be transmitted by a virus came from Ellermann and Bang who showed that leucosis of fowls could be transmitted to similar birds not only by injecting leukaemic cells, but also by injecting cell-free filtrates. In the case of mammals no such cell-free transmission could be demonstrated. Rous in 1910 described a transmissible fowl sarcoma that could be propagated by cell-free filtrates after several initial passages by grafting. Murphy, working with Rous in 1911, showed that the same tumour could be transmitted by means of extracts of desiccated tumour. At about the same time Fujinami made similar observations independently. In the following eight years, Rous and his colleagues described a number of fowl tumours, all of mesoblastic origin, which could be transmitted by means of cell-free filtrates, or desiccates. Several different histological types were represented, and in each case the cell-free extract faithfully reproduced in the new host the histology of the original tumour. In 1929 Fujinami successfully transferred his filtrable chicken tumour to ducks, but in these birds, although the tumour has the same histology as it has in fowls, spontaneous regression occurs regularly. In 1933 several independent workers (Oberling and Guerin; Furth; Rothe Meyer and Engelbreth-Holm) showed that the virus of leucosis in fowls could also induce sarcoma in a minority of birds inoculated, depending upon the site of injection of leukaemic blood. McIntosh in 1933 noticed a similar relation between leucosis and sarcoma occurring in fowls grafted with tumour tissues from birds that had received injections of tar. The majority of fowl tumours induced by means of chemical carcinogens show, however, no association with leucosis and are not transmissible by cell-free extracts. Epithelial tumours of fowls are known to occur spontaneously but no cell-free infective agent has been demonstrated in relation to such tumours.

In 1932 Shope described two new transmissible neoplastic diseases affecting wild cottontail rabbits; one was a fibroma of the subcutaneous tissues, the other a papilloma of the hair-bearing skin. Both lesions could be transmitted in series in cottontail rabbits by inoculation or scarification with cell-free extracts, and both could be transferred from cottontail to domestic rabbits, but could not originally be serially transmitted in the latter species. The tumours are benign and tend to regress, but

Subsequently Cook and his colleagues synthesized a large number of new polycyclic hydrocarbons and chemically related substances and established many interesting associations between their molecular structure and biological properties. One of the most potent of these substances, 20-methylcholanthrene, is particularly interesting because of its chemical relationship to bile acids and cholesterol, from which it can be prepared in the laboratory. It has not yet been demonstrated, however, in extracts of animal tissues or tumours. In recognition of these achievements by the staff of the Research Institute of the London Cancer Hospital, a prize of 50,000 francs and 50 milligrams of radium was presented jointly to Professors Kennaway and Cook by the International Anti-Cancer Union at Brussels in 1936. In a little over ten years some 700 chemical substances have been tested of which 169 are listed by Hartwell as being carcinogenic, apart from twenty-three said to cause papillomas. The whole subject of chemical carcinogenesis was reviewed by Kennaway and Cook in 1937, 1938 and 1940.

Azo-compounds

At about the same time as the discoveries of carcinogenic polycyclic hydrocarbons were made, Yoshida in 1932 described liver tumours in rats fed on *o*-aminazotoluene (non-staining scarlet). Independent work has confirmed and extended his observations and a number of azo-dyes are now known to be capable of inducing various types of primary liver tumour, some of which are malignant. Several of these substances also induce sarcoma at the site of injection. In this type of carcinogenesis, diet has been found to play an important part. In particular, deficiencies of riboflavin predispose to the development of hepatoma, which is often—but not necessarily—associated with cirrhosis, as is the case in human beings. Animals can be protected, at least partially, against the action of the azo-carcinogens by making good various dietary deficiencies or by augmenting the diet. The subject is too complex for further discussion in a short article. A different type of carcinogen was discovered by Browning in 1933 while he was investigating trypanocidal drugs. The substance, styryl-430, is water soluble, unlike most other known carcinogens, but in combination with proteins, forms a precipitate in the tissues. It is not at all readily absorbed in the form mentioned, but slowly excites a marked macrophage reaction from which sarcoma may originate after a latent period of many months. Hitherto unsuspected carcinogenicity was discovered by Wilson, DeEds and Cox in 2-acetaminofluorene (known since 1884), which was being tested as an insecticide.

Physical carcinogenesis

Ultra-violet rays, x-rays, and the rays of radium or thorium have all been shown to be carcinogenic in certain circumstances. Cancer may also ensue after superficial burning and after scarring due to freezing with solid carbon dioxide. Such tumours resemble, in a general way, chemically induced cancers.

a benzene extract of the liver taken from a case of fatal gastric cancer. Subsequent independent work confirmed the presence of lipid-soluble non-saponifiable carcinogens in the livers of some cancer patients and less frequently in the livers of non-cancer patients. The chemical nature of this type of carcinogen has not yet been established, but the experiments of Des Ligneris suggest that the factor may be of aetiological importance in those Asiatic and African peoples who have a high rate of incidence of primary liver cancer. Steiner has reviewed this very interesting branch of research.

The mechanism of carcinogenesis

As soon as pure chemical carcinogens became available, the study of the way in which the body reacts to these substances became possible. It was particularly fortunate that the first carcinogenic hydrocarbons to be discovered had the very characteristic fluorescence already mentioned. I made use of this property in 1936 for the purpose of following the fate of benzpyrene and other hydrocarbons after their injection into animals. Benzpyrene is rapidly absorbed by the liver from the blood stream and is excreted in a modified form (BPX) in the bile. BPX was isolated by Chalmers and myself and was partly identified by Chalmers and Crowfoot as a monohydroxybenzpyrene. Berenblum and Schoental finally identified BPX as 8 hydroxybenzpyrene and later found it to be weakly carcinogenic as compared with benzpyrene. BPX is more easily soluble in body fluids than is the parent hydrocarbon. It was already known that the mere presence of a carcinogen in the body was not always sufficient to induce a tumour, and in 1935 I showed that the solvent used as a vehicle might play a determining part. This observation was extended in collaboration with Beck, and has been independently confirmed. Thus it is apparent that the body is not defenceless against the effects of chemical carcinogens, which it may be able to absorb, metabolize, and finally eliminate under favourable conditions. Chemical carcinogenesis seems to depend upon the maintenance of an optimum concentration of carcinogen for an optimum time in a susceptible site. Significant statements about carcinogenic potency of a substance must include details of the solvent used as the vehicle, the species of animal and the site of application.

Co-carcinogens and anti-carcinogens

Although irritation in a general sense is not a cause of cancer, yet a number of irritants exercise a modifying effect on experimental carcinogenesis. Berenblum showed that mustard gas in very dilute solution painted on the skin of mice rendered the skin refractory to the action of chemical carcinogens. Such an effect is uncommon. Many irritants, however, have an opposite effect and enhance the action of carcinogenesis. Recent work by Berenblum and by Mottram has thrown fresh light on the pathological processes involved and may help to explain the occasional apparently causal relationship between trauma or infection and subsequently occurring cancer.

Tumour inhibitors

The inhibiting substances described by Haddow, to which reference has been made, differ from anti-carcinogens in that they act on established tumours.

COMMENTARY

In the foregoing brief review controversial work and purely theoretical discussions have been avoided. The facts are not in dispute, but their interpretation often is, and it may be of interest to present the picture as it appears to me, with the admission that there are other ways of looking at the same facts. Cancer begins as a local disease of one or more cells and can be experimentally initiated in a variety of ways. As seen in human subjects the causal factors are usually obscure. No common factor has yet been demonstrated which can be called the cause of cancer. Analogy with other disease processes suggests that no such common cause will be found. Our method of classifying cancers is based on their histology. If we adopted the same method of classifying other diseases, for example inflammatory diseases, we should not be able to point to a unit cause any more certainly than we can in the case of cancer. Cells have a limited range of expression and many different types of pathogenic agent can elicit the same type of cellular response. One of the most characteristic features of cancer is the apparently irreversible nature of the change that occurs in a cell when

it becomes malignant. The daughter cells continue to reproduce the characteristics of the parent cancer, even when they are remote from the original exciting cause. As an explanation of this, many pathologists favour the theory originally advanced by Boveri, that the malignant cell has undergone a mutation. It is characteristic of mutant cells that they reproduce faithfully their altered characteristics unless they are subjected to a further mutation. The filtrable principle which can be extracted from a few animal tumours and is regarded by many investigators as a virus, may equally well be an intrinsic product of the tumour; for this reason the principle has been described by Murphy as a "transmissible mutagen". The behaviour of the filtrable tumours, however, suggests that they differ in some essential way from the majority of cancers, particularly in those cases which undergo spontaneous regression. The presence of a virus in the nucleus of a cell might initiate the process of cell division and the daughter cells, if contaminated in the same way, might undergo the same process indefinitely, as long as the virus persisted. If the cell has not undergone any mutation, however, the disappearance of the virus would leave the cell essentially a normal cell which might be expected to conform once more to the physiological control of the body. Spontaneous regression is not uncommon in experimentally propagated virus tumours, but is rare in chemically induced cancers. Histological examination has not revealed any difference between the morphology of a tumour that contains an active "virus" and another tumour of the same origin from which no such "virus" can be extracted. The only certain way of demonstrating the presence of virus is by inoculation in animals; this clearly cannot be practised in human beings. There is no reason to suppose, however, that the reactions of human beings differ essentially from those of lower animals, and in the case of industrial cancers we know that the same agents can cause the same histological types of tumour both in man and in lower animals. If it is a fact that a few tumours in animals are attributable to "virus" infections, there are no grounds for the presumption that viruses never play a part in the aetiology of tumours in human beings. In the face of all the evidence, however, it is unreasonable to assume that cancer in general is due to viruses and there is ample evidence that tumours in man can be caused by chemical carcinogens. Moreover, statistical evidence shows that certain types of cancer affect human beings in different parts of the world in a way not readily explained on genetic grounds. For instance, cancer of the stomach is twice as common in many European countries as it is in Great Britain. Human beings differ from other animals in the extent to which they subject themselves to unnatural environmental conditions, some of which entail known carcinogenic risks. The danger of exposing human beings to untested chemical substances is well illustrated in the case of the apparently non-toxic substance 2-acetaminofluorene which might have been used as an insecticide had it not been shown to be a carcinogen. It is probable that other avoidable causes of cancer will be discovered but it is already clear that conventional toxicity tests afford inadequate protection against potential carcinogens. Legislation may be necessary to prevent the use in commerce of chemical substances which have not been submitted to tests for carcinogenicity.

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EAR, NOSE AND THROAT DISEASES

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CARCINOMA OF THE LARYNX

Surgery

The surgical treatment of intrinsic carcinoma of the larynx presents no longer any unsolved problem. For all conditions in which the disease is confined still to the larynx an appropriate operation is available, thus for example in an early case in which one cord is affected the operation of laryngofissure is suitable. When the anterior commissure is invaded or when the growth sits astride the cords in this situation a modified hemilaryngectomy, whereby the front of the larynx is excised, is appropriate. In more advanced cases, when one half of the larynx is fixed, when both cords are invaded, when the growth is subglottic or when the growth has arisen in or extended to the ventricles or epiglottis, total laryngectomy is required. The chief risk of these operations arises from septic complications, especially in total laryngectomy, owing to the proximity of the pharynx and the mouth to the wound. Chemotherapy has now almost abolished this risk, so that with proper technique the mortality rate in these operations is now very low. In a series of 23 cases of laryngofissure or partial laryngectomy 18 patients (78 per cent) survived 10 years or more, and in 75 cases of laryngectomy for more advanced disease 45 patients (60 per cent) survived more than 10 years (Colledge). At present with improved technique the results should be rather better.

Radiotherapy

Radium needles—There are, however, many elderly and rather frail people amongst those who are attacked by this disease, and it is not rare to encounter arterial degeneration, chronic bronchitis or other pulmonary disorder and occasionally alcoholism. In patients of this type radiotherapy would naturally be preferred if it offered a reasonable prospect of success, and the problem now presented by cases of carcinoma of the larynx is whether operative treatment or radiotherapy should be recommended. Harmer has reported that, as a result of the implantation of radium needles in the side of the larynx after resection of the thyroid ala, in 24 early cases 14 patients (58 per cent) and in 72 advanced cases 32 patients (44 per cent) survived three years.

The results of this form of radiotherapy are therefore inferior to those of excision, although many patients have remained free from recurrence, with a good voice. There seem to be two main reasons for the restriction of possible success in the treatment with needles. (1) Not only is it difficult to fix a row of needles in position and to maintain them there for several days without movement so that a constant field of irradiation is preserved, but also, as Lederman and Mayneord have shown, with the usual arrangement of the needles the distribution of irradiation in the horizontal plane is heavy at the anterior commissure, but falls off rapidly along the cord towards the arytenoid cartilage. These calculations were made from an arrangement in which 10 milligrams of radium were used, four 2 milligram needles being placed vertically, with two 1 milligram needles crossing the ends. Morton, Gray and Neary have since confirmed these observations by a similar investigation in which it was shown that the amount of radiation received by the anterior end of the cord is double that at the posterior end. There is therefore not a homogeneous irradiation of the tumour unless it is quite small and is confined to the anterior part of the vocal cord. (2) It is at present not possible to tell in advance whether a tumour is radiosensitive or not. Although histological examination shows fairly accurately the degree of malignancy of a tumour and therefore is of value to the surgeon in prognosis as well as in diagnosis, it does not provide any information concerning radiosensitivity, nor have any of the factors which make for radiosensitivity been discovered. The more

malignant (that is the more cellular and less differentiated) tumours are not, as was expected, necessarily the more radiosensitive, and sometimes they prove to be just the opposite. There is at any rate a large proportion of epitheliomata which are radio-resistant and therefore the use of radiotherapy involves a gamble, the chances of which have not been exactly calculated.

Teleradium.—If the second limitation to the value of radiotherapy is still beyond control, the difficulties associated with radiation by needling can be overcome by employment of teleradium. A beam of radiation from 5 grammes or more of radium is directed on the larynx from different points according to the requirements of the case, the technique being adaptable instead of fixed and standardized, as treatment with needles must be. In this way a full dose of radiation can be administered to the entire volume of tissue which it is desired to irradiate without any attempt being made to preserve the principle of homogeneous irradiation. This method is more prolonged; the full treatment, in protracted fractional doses, lasts for about six weeks. The constitutional reaction, however, in contrast to the malaise which often follows deep x-ray therapy, is slight, and so also is the reaction in the skin. The method has the advantage that there is no operative risk, that there is no wound liable to sepsis and that the reaction to the radiation can be observed during the course of the treatment. It is hoped by doing this to overcome the second limitation already mentioned, because if it is soon apparent that the tumour is radioresistant the treatment can be stopped and the case can be treated surgically. Neilsen and Strandberg in Copenhagen and Cutler in Chicago have therefore suggested a therapeutic test in order to determine whether the tumour is radiosensitive, in which case a full course of radiotherapy is given, or whether it is radioresistant, when the unsatisfactory response is regarded as an indication for operative treatment by excision. The radiotherapist must, however, have the moral courage to break off treatment in such circumstances; he must not be tempted by the hope that more radiotherapy will overcome the radioresistant character of the tumour. It is doubtful whether such experimental treatment with so powerful an agent as radium can be justified; Cutler believes that it can be, and is of opinion that subsequent surgical treatment is not much prejudiced by its employment. It is certain, however, that although some wounds heal satisfactorily after radiotherapy, in many cases operation is hazardous and difficult: the healing is always prolonged; some wounds never heal; a few patients succumb to secondary haemorrhage; plastic operations are either failures or have to be completed in many stages.

Using treatment by radium beam (or teleradium), Lederman has been able to report as follows from the Royal Cancer Hospital, London. Out of 8 cases of early carcinoma 6 patients are living free from symptoms—2 of them for more than 5 years; out of 15 more advanced cases which would have required laryngectomy, 12 patients are living free from symptoms—6 of them for more than 5 years and 3 more for more than 2 years.

It may be concluded, therefore, that if the choice of treatment falls on radiation, teleradium should be preferred to treatment by radium needles, although the latter method still has its advocates. It seems to be wiser to decide only after careful consideration of all aspects of the case whether to recommend surgical treatment or radiotherapy to the patient, first consideration being given to excision as providing the better prognosis; the radiotherapists do not agree to this, claiming that radiotherapy merits first consideration because of its non-mutilating effects and the absence of operative risk. Certainly exploratory laryngofissure to determine the extent of a growth in a doubtful case should be avoided at all costs, and it is probable that not many more years will pass before the use of radium needles comes to be regarded as an anachronism.

BAROTRAUMA

Paul Bert in *La Pression Barométrique*, published in 1878, mentions that pain in the ears can be produced by both compression and decompression, that is to say that such symptoms have been experienced by workers in diving bells and in caissons and also by mountain climbers and aeronauts. Some of the symptoms are due to the physiological effects of alterations in the partial pressure of the oxygen, but the pain in the ear is primarily due to mechanical pressure on the tympanum, so that the physiological and mechanical effects have to be differentiated. Moreover, it is now recognized that hyperpnoea from a lowered partial pressure of oxygen also has an

effect on the content of carbon dioxide in the blood, which in turn affects the respiratory centre. The mechanical effect on the ear is now rather neatly expressed by the word, barotrauma, and some reference to it, and especially to the work of Armstrong and Heim on the physiology of the pharyngotympanic (eustachian) tube, was made in *Surveys and Abstracts* 1940, p. 48. The subject has proved to be so important to the Royal Air Force in action that some further description is permissible.

Effects on aviators

Towards the end of World War I, Scott made clinical observations on the ears of pilots in the Royal Flying Corps at a time when greater heights were being reached and when resultant effects of changing altitude on the middle ear had become more noticeable and more disabling. He observed that ill effects occurred only during descent, and could usually be avoided by keeping the tympanum periodically inflated through the pharyngotympanic tube, although sometimes pain and deafness could be relieved only by use of the eustachian catheter. Scott observed various degrees of congestion of the membrane and occasionally rupture. He recommended that "Airmen should not fly with a cold in the head, sore throat or when unable to inflate the eustachian tubes at will." Experimental observations by Armstrong and Heim, however, laid the foundation of accurate knowledge of the physiology of the pharyngotympanic tube in relation to aviation. Five healthy men were subjected to changing rates of pressure varying from 5.4 to 27 millimetres of mercury per minute, corresponding to 200–1,000 feet of altitude per minute, through ranges of pressure from 760 to 141 millimetres (0–46,000 feet of altitude). By decreasing the pressure from sea level (760 millimetres) at a constant rate it was found that a change of 3–5 millimetres of mercury (110–180 feet of altitude) was required to produce any effect. Discomfort increased until at 15 millimetres of mercury (500 feet of altitude) an involuntary click was felt and the sensation of fullness in the ears was relieved. Succeeding clicks occurred at intervals of 11.45 millimetres of mercury (435 feet of altitude). The pharyngotympanic tubes therefore open involuntarily during ascent and equalize the intratympanic pressure with the atmospheric pressure. In descent, however, the tubes were found to remain closed under all degrees of pressure and the tympanic membrane finally ruptured unless the tubes were opened by an act of swallowing, such opening becomes impossible and the tube is locked when a negative pressure of 80–90 millimetres of mercury is produced in the middle ear. Frequent voluntary acts of swallowing are therefore necessary to maintain equilibrium during descent. Inflammatory changes are secondary to the injury caused by these strains and stresses.

Barotrauma has played an important part in the maintenance of efficiency in air crews since heights of 40,000 feet and more have been reached and the effect on the ear has been further studied both clinically and in pressure chambers. Pain, deafness, tinnitus and occasionally vertigo are the symptoms, and they are relieved when the equilibrium is restored by swallowing, by Valsalva's experiment, by politizerization, by eustachian catheterization, by reascent or by decompression in the chamber.

Campbell recommended the last method in severe cases because the pressure outside the tympanum and of the air passing through the pharyngotympanic tube are altered simultaneously, whereas in politizerization or catheterization only the pressure of the air entering the pharyngotympanic tube is altered. Paracentesis is contra-indicated.

There may be little objective sign, but at first the tympanic membranes become sharply retracted, and the vessels along the handle of the malleus become engorged. Soon there is an ecchymosis into the flaccid part of the tympanic membrane (Shrapnell's membrane) and various degrees of engorgement of the tympanic membrane ensue. Haemorrhages, effusion into the middle ear with bubbles during recovery and even rupture of the membrane, have been observed by McGibbon.

The cardinal factor in the production of the effects mentioned is eustachian obstruction, which at ground level may not cause more than trivial or negligible symptoms. Consequently a mild degree of eustachian obstruction is a contra-indication to flying, for then barotrauma may be produced by descent from a high altitude, and it is temporarily disabling.

Matthews has pointed out that in practice not only is the individual disabled but also the crew of which he is a member may be disabled if he himself cannot go into action even for one day. Clinical examination and testing in the decompression chamber facilitates the elimination of those particularly liable to barotrauma. Dickson

has estimated these at 8.9 per cent. It is obvious that preventive measures against the spread of infectious coryza are needed in order to check the incidence of pharyngeal catarrh and in these circumstances the decision whether a member of an air crew may or may not fly when he has a cold, is a matter of some responsibility.

Barotrauma and the accessory sinuses

Barotrauma also affects the accessory sinuses in a similar but not identical fashion. If the ostium of one or more of these cavities is obstructed by a polyp or swollen mucous membrane the changes in atmospheric pressure cannot be equalized. During ascent the pressure inside an obstructed sinus becomes greater than that outside it, with expansion of its walls to the limit of their elasticity. This causes pain, especially in the frontal sinus. During descent the effect is reversed, but a polyp may form a ball valve over the ostium, or pus may be sucked into a sinus. In this way the negative pressure in a sinus may tear the mucous membrane from the bone, with resultant haemorrhage and effusion into the cavity.

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ACUTE INFECTIVE DISEASES

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EPIDEMIOLOGY IN THE TWO WORLD WARS

As Great Britain has now emerged from five and a half years of total war in the European theatre affecting every section and activity of the community, a review of the epidemiological position in World War II as compared with that of World War I is inevitable. On balance there can be little hesitation in conceding that World War II can bear the comparison in most respects. On the credit side it has escaped those two great scourges of the first world war, epidemic influenza and encephalitis, and although strictly comparable data for the two war periods are not available there are solid grounds for believing that mortality from scarlet fever, measles and whooping cough has fallen significantly although not to the same degree as that from diphtheria. On the debit side, cerebrospinal fever has been nearly four times as prevalent (but as the case fatality was reduced to one-fourth the mortality remained about the same), dysentery and salmonella infections, generally mild in character, reached a high level of prevalence due to an almost continuous series of local outbreaks rather than to a tendency to widespread epidemicity, while both infantile and neonatal diarrhoea tended to increase in prevalence and severity with each year. On the other hand, the enteric fevers have become distinctly less prevalent, judging from the almost identical case mortality of approximately 10 per cent in 1918, 1943 and 1944, the proportion of typhoid to paratyphoid infections has probably remained about the same. In the table below are detailed the notifications of the principal notifiable diseases in England and Wales in the years 1918, 1943 and 1944, the case fatalities (in brackets) for 1918 apply to the whole country, but for 1943 and 1944 they apply only to the 126 great towns. The figures for 1937-1943 appeared in Medical Progress (Critical Survey section) 1945, p. 35.

ENGLAND AND WALES			126 GREAT TOWNS	
1918			1943	1944
Diphtheria	-	43,678 (10.99)	35,944 (3.59)	29,446 (2.79)
Scarlet fever	-	48,170 (2.12)	116,217 (0.12)	93,801 (0.13)
Measles	-	-	374,198 (0.25)	117,437 (0.18)
Whooping cough	-	-	95,859 (1.23)	93,107 (1.23)
Typhoid fever and Paratyphoid fever	-	4,232 (10.04)	707 (10.1)	536 (10.1)
Dysentery	-	-	7,772 (-)	10,150 (-)
Cerebrospinal fever	-	798 (101.75)	3,380 (-)	2,883 (-)
Acute pneumonia	-	-	52,225 (-)	38,175 (-)
Influenza	-	-	-	-
Deaths	-	112,329	6,280	1,744
Diarrhoea and Enteritis under 2 years of age	-	-	-	-
Deaths	-	-	2,569	2,610
Dysentery (bacillary and amoebic) and	-	-	-	-

Dysentery (bacillary and amoebic) and pneumonia were made notifiable in 1919, measles and whooping cough in 1939.

Deaths from diarrhoea and enteritis in children under 2 years of age rose steadily each year after the outbreak of the war, despite certain improvements in treatment discussed below. The causes of the rise in fatality—and almost certainly in incidence although exact figures are unavailable since the disease is not generally notifiable—are various: increasing aversion or inability to breast feed, transfer of maternal duties to unskilled attendants or to day nurseries hastily improvised and

frequently lacking adequate facilities for segregation of potentially infectious subjects; care of babies in residential institutions, especially illegitimate and deserted babies or those neglected on account of war duties or distractions, or because of unfavourable home environment. In a recent study of the influence of social conditions on infant mortality in the county boroughs of England and Wales, Woolf and Waterhouse concluded that of the 250,000 deaths of babies in the 11 years 1928-1938, about 63 per cent were attributable to adverse social conditions; of the preventable deaths one-third were associated with overcrowding, one-quarter with ill-paid occupations, one-fifth with unemployment and one-eighth with the industrial employment of women.

It is generally assumed that our highly gratifying but rather unexpected freedom from a major influenza epidemic during World War II is attributable to the improved nutritional and hygienic conditions of the community at large as compared with those of World War I; if this were the whole story it hardly explains a like freedom in occupied countries and among prisoners of war and displaced persons in Germany who lived under very unfavourable conditions. Nor can absence of infection and mere chance be wholly responsible, since influenza A did appear in epidemic form in the winter-spring months of more than one of the war years; it failed to establish itself, however, as a widespread killing disease, hardly affecting the young adult population, attack amongst whom was a conspicuous feature of the 1918-1919 series of epidemics. Active immunization with vaccines made with virus alone or in combination with secondary invaders has generally failed of its purpose, the resulting immunity being uncertain and transient, but a more recent experience (Hirst, Rickard and Friedewald) of a concentrated type of virus vaccine suggested that protection lasted for as long as a year. Increasing attention has been paid to the role of the nasal mucosal barrier and the part played by its protective secretions which may neutralize not only influenza virus but also a number of other respiratory pathogens. Although increase of nasal antibody may result from inoculation, its concentration is not necessarily correlated with the blood titre. Probably the coexistence of other catarrhal infections, of fatigue and of exposure to extremes of temperature are as important in influenza and in poliomyelitis as they are known to be in cerebrospinal fever, but the improved therapy and prophylaxis of the latter (a short course of a sulphonamide rapidly abolishes the carrier state) must be conceded to play a significant part in control. In a recent review Stuart-Harris has admitted that despite intensive research the influenza enigma remains largely unsolved. Poliomyelitis was relatively infrequent in occurrence in World War II compared with the years immediately preceding it, and especially as compared with 1918. This may be taken to support the view that it is not, in Great Britain at least, usually an ingestion disease, since dysentery and salmonella infections have been particularly rife although the recorded increase of these diseases is perhaps partly artificial due to advances in cultural technique, to improved bacteriological facilities, especially in rural districts, and to wider appreciation of the clinical and epidemiological features of these disorders. The reduction in diphtheria mortality, more striking even than reduction in incidence, is naturally attributed to active immunization, but caution is needed in forming a final opinion since the favourable results of dispersal through evacuation and other war conditions cannot be fully determined until the effects of re-aggregation have been fully observed. Particularly it needs to be emphasized that a low mortality is no excuse for slackening of effort in immunization campaigns.

IMMUNITY AND CHEMOTHERAPY

Action and interaction in disease

In the half-century preceding the discovery of sulphonamide therapy (1935) infective processes were combated in the absence of specific drugs by various supportive measures and by injection of such preformed antibodies as were available. Generally speaking, in therapeutics antibacterial sera were less successful than were antitoxic sera, partly by reason of the essential character of the disease processes and partly by reason of the necessity for providing type-specific antibody, which last frequently entailed some delay in administration; in some instances, such as cerebrospinal fever, it might even be necessary to postpone preparation of immune serum until the current epidemic strains are isolated. At present diphtheria is the only infective disease in which antibodies are regarded as a therapeutic necessity; penicillin has

been used as an adjuvant in severe gravis infections but not so far solely in treatment, although it may well prove to be adequate, especially for the less severe forms in individuals known to be serum sensitive. Theoretically there is a strong *prima facie* case for preformed antibodies, both antitoxic and antibacterial, in the treatment of severe infections with an overwhelming toxæmia, whether the infection is streptococcal, staphylococcal, pneumococcal or meningococcal, since neither sulphonamide nor penicillin has been shown to have a neutralizing action on toxins. It would appear, however, that toxin is fixed to the body cells or is neutralized so rapidly that mere inhibition of toxin production, if it is promptly effected, suffices in the great majority of cases. When severe metabolic or somatic damage threatens life, non-specific anti-shock measures are nowadays the fashion but it has not been shown decisively that these could not be augmented by specific serotherapy.

The theory of drug neutralization has been more or less superseded by that of competitive avidity which postulates physical and chemical changes which may vary according to the particular drug, its effective concentration, the bacterial species involved and the reactions of the host. Thus, Marshall has shown that mice treated with sulphonamides tend to react differently according to the invading organism: to streptococci by development of phagocytosis, to pneumococci by production of antibodies which may *in vitro* convert the normally bacteriostatic action of the sulphonamide into a bactericidal one. Probably competition between drug and *p* aminobenzoic acid leads to complex changes in bacterial metabolism, which under optimal therapeutic conditions lead to death of the organism but under other conditions may enable it to dispense with this food factor and so induce drug resistance which may be transmissible to succeeding generations.

The exact mode of action of penicillin is unknown but it appears to prevent multiplication of bacteria which take on aberrant shapes, usually elongated or bulbous, prior to dissolution of the cell by natural ageing or phagocytosis. Bacteria are apparently particularly vulnerable in the lag phase of growth which, far from being, as originally thought, a period of inactivity, is a phase of rejuvenescence characterized by rapid increase in respiratory and metabolic activity and in enlargement of individual cells prior to division. A proportion of the bacteria in a pure culture may not undergo normal evolution during this phase and may therefore remain temporarily insusceptible to the action of penicillin, to these Bigger² applied the term, *persisters*, to distinguish them from drug resistant organisms (*resisters*). It is unlikely that its exact pharmacological action will be established until the chemical nature of penicillin is determined, or the reasons known why in some circumstances sulphonamides appear to interfere with its activity, although in regard to the latter, some investigations point to the existence of a synergistic action (Bigger¹). The influence of these drugs on antibody production is equally obscure, it is probable that the rate of production is lowered as the invading organisms are killed or rendered inert, and may be further lowered if damage to the haemopoietic system is inflicted by excessive dosage with sulphonamides, on the other hand, it has not been proved that the widespread use of the drugs has resulted in a general lowering of individual or herd immunity (bacterial as distinct from viral immunity) or that there is positive antagonism between them and preformed antibodies.

The fundamental researches on plasma proteins initiated by Cohn at Harvard and later carried out on a large scale with the collaboration of a large team of workers (Cohn and his colleagues) may make an important contribution to this subject. By means of the ultracentrifuge and electrophoresis apparatus the proteins of pooled human plasma collected from several thousands of donors were divided into its component fractions, which these workers investigated by biological, chemical and physical methods, including the use of elaborate optical systems. Normal plasma consists of 55–60 per cent of albumin, upon which approximately 80 per cent of its osmotic activity depends, but contains no demonstrable antibody, it is therefore of particular value in combating shock, being in a 25 per cent saline solution practically isoviscous with human blood. Although globulin constitutes nearly 38 per cent of plasma protein, the most important antibodies are confined to a particular kind designated γ -globulin, which forms only about 11 per cent of total proteins, this substance has been isolated on a commercial scale in almost pure state, but for clinical use the solution, in which the protein content is fixed at 16.5 per cent \pm 1.5 per cent, represents approximately a 25 fold concentration of the parent plasma.

The substance has been shown to possess antibodies to a large number of infections; so far its use has been confined to the prophylaxis and treatment of measles (volume for volume, it is about twice as potent as is convalescent serum) and to the prophylaxis of infective jaundice (Stokes and Neefe), but it is likely to possess antibodies in protective titre against a number of infective diseases such as mumps, chickenpox, whooping cough and poliomyelitis for which convalescent sera have hitherto proved to be disappointing. The investigations of Brand, Kassell and Saidel showed that, compared with the immunologically inert albumin, γ -globulin is rich in the sulphur-containing amino-acid tryptophane (α -amino- β -[3-indolyl] propionic acid) and the hydroxyamino-acids tyrosine (*p*-hydroxyphenylalanine), serine and threonine and hydroxyproline, but contains fewer basic groups and disulphide linkages. Methionine, which has a detoxifying or protective action on the liver, is absent from horse albumin but is present in human albumin although the amount is considerably lower than it is in γ -globulin. Although it is not yet possible to correlate amino-acid constitution with physicochemical and immunological properties it is probable that the number and arrangement of the polypeptide chains (often referred to as sub-units and likened to the bricks of which the protein molecule edifice is built), of which γ -globulin has 25 and albumin 36 per molecule, and their interaction with each other and with their medium, largely determine their behaviour. Disintegration of globulins by acid hydrolysis or enzyme digestion below the polypeptide stage is known to destroy their immunological properties.

Whether the antigen-antibody reaction follows the law of mass action or, as is more probable, is an adsorption phenomenon, it does appear that antibody introduced into the body can prolong the bacterial lag period and may even evoke a stationary phase rendering organisms insusceptible to drugs; variations in natural antibody production (which probably depends upon protein storage and hepatic efficiency) can conceivably lead to a similar effect with consequent production of bacterial persisters and resisters. Nutrition and preformed antibodies have therefore more than an academic interest and may ultimately be found to have a direct bearing on the dosage and mode of administration of both penicillin and the sulphonamides—which are further complicated by the toxicity factor.

PENICILLIN IN INFECTIVE DISEASE

Considerations of supply have hitherto largely governed the use of penicillin in infective diseases. Some invasions are so sudden and overwhelming that if lives are to be saved it must be employed at once instead of waiting, as is still enjoined, until the invading organism is proved to be sulphonamide-resistant and penicillin-susceptible. Bacterial susceptibility varies widely from the highly susceptible gonococcus to the practically resistant *Eberthella typhosa*; it is therefore more logical to correlate blood levels of the drug with the susceptibility of the invading organism instead of with a highly susceptible standard organism. The patient's response is an even more reliable index of therapeutic efficiency. As supplies become more abundant dosage will undoubtedly increase, since high concentrations are now proved to be bactericidal, not merely bacteriostatic; greatly purified samples practically never cause thermal reactions but, contrary to expectation, tend to produce venous thrombosis, which strangely enough has been found to be less common in young children than in adults. In contrast with sulphonamides, which are rapidly and more or less evenly distributed throughout the body tissues and fluids, penicillin does not readily pass through mucous or serous membranes even when their integrity has been damaged by inflammatory processes. Local application is therefore the mode of choice, as for instance intrathecal administration in pyococcal meningitis (the solution should be dilute, about 1,000 units per cubic centimetre), but in severe infections, in which septicaemia is a common antecedent or concurrent accompaniment, systemic injection is indicated in addition and may be the decisive factor in saving life, especially in streptococcal and pneumococcal infections. The primary focus, often mastoid or sinus disease, as well as sequelae such as pyelitis or osteomyelitis, must be dealt with suitably.

The vexed question of systemic administration has not yet been settled. Although the intermittent muscular route remains the favourite despite the disadvantages of pain (relieved by added 1 per cent procaine hydrochloride to the inoculum) and the

necessity of waking a sleeping patient, increasing use is being made of continuous or intermittent administration through a needle placed deeply into the vastus lateralis, using some 100–200 cubic centimetres of solution according to dosage, which usually ranges from 100 000–250,000 units for adults (approximately 1,000 units per pound of body weight) in 24 hours. Successful oral administration with alkalis and raw egg (Little and Lumb), or buffered with trisodium citrate (György and his colleagues), or in acid resisting capsules (Florey and Florey), have been recorded, but this route has not established itself as being sufficiently reliable for really severe infections. Other methods include devices to slow absorption from the tissues by incorporating the drug in a beeswax peanut oil medium (Romansky and Rittmann), or by previously chilling the muscle with an ice bag (Trumper and Hutter), or by delaying excretion by the giving of diodrast (diodone) (Rammekamp and Bradley), or *p* amino hippuric acid (Beyer and his co workers), but none has been sufficiently tried even for a tentative assessment of relative efficiency. The clinical impression that penicillin does not exert any action against virus infections has been confirmed by the laboratory tests of Parker and Diefendorf on a number of viruses, including those of psittacosis and vaccinia.

Local application of sulphonamides and penicillin in buccal and upper respiratory tract infections generally, has as yet been insufficiently explored. Vollum and Wilson have recently shown that sulphonamides in lozenge form reach the tonsils rarely or in concentrations so weak as to be ineffective. On the other hand, MacGregor and Long found penicillin pastilles—500 units in each gelatin pastille, which lasted for about 45 minutes the pastilles being given continuously by day—to be of value in gingivostomatitis (Vincent's angina) and in streptococcal tonsillitis, symptomatic relief and rapid elimination of pathogens were effected but trials were few and proper controls were absent. In young children the nasopharynx is a more dangerous infective focus than are the tonsils and is more readily reached by nasal instillation of penicillin, this is given in a solution of 500 units per cubic centimetre, to which 2 per cent phenoxetol is added in order to inhibit coliform bacilli and like organisms which tend to neutralize the drug by production of penicillinase. American workers have found the systemic administration of sulphadiazine to be effective in preventing the secondary infections of colds and catarrhal infections. Coburn has significantly reduced the incidence of streptococcal tonsillitis and rheumatic complications and has also cleared up the carrier state in young naval recruits, among whom these diseases interfered to a serious extent with the war effort, he found it necessary to give sulphadiazine, 1 gramme daily, for periods of weeks or even months, when respiratory infections were prevalent, instead of for a few days—the period usually sufficient for meningococcal carriers. Sensitization and toxic effects were not commonly experienced. Although such effects are very rare with penicillin, instances occasionally come to light (Barker).

AMINO-ACID THERAPY IN INFANTILE DIARRHOEA

Although considerable improvement in the fatality rate of infantile diarrhoea resulted from routine use of human plasma in the endeavour to restore disordered metabolic functions (Alexander and Eiser) persistent vomiting and diarrhoea may lead to a state of tissue starvation which may prejudice recovery. If too much plasma is given there is a tendency for tissue fluids to pass into the circulation, with resultant circulatory overloading and cardiac embarrassment. Generally 1 part plasma to 3 or 4 parts glucose saline or Ringer lactate solution suffices to maintain the normal colloid osmotic pressure of the blood, but in this concentration it gives only 2–3 grammes instead of the normal 4 grammes of protein per kilogram of body weight which are required in twenty four hours. When oral feeding is impossible the plasma may be supplemented by amino-acids introduced directly into the vein. Shohl showed that a positive nitrogen balance could be maintained in infants by combined intravenous and oral administration of casein hydrolysates (containing the principal amino acids necessary for nutrition and growth) until ordinary feeding is re-established. The method is not free from risk and as these materials will doubtless be available now that hostilities have ceased, my own experience of it may be of some assistance. (Gunn) An acid hydrolysate is preferable to an enzyme digest because the process of protein disintegration is more complete and less likely to cause thermal reactions,

for intravenous use the hydrolysate should be prepared by the makers in solution (10–20 per cent is convenient) and should be diluted to 2·5 per cent for administration, since the powder is hygroscopic and is prone to bacterial contamination which may elaborate pyrogenic metabolites not destroyed by sterilization. The use of plasma appears to be an important factor in preventing the venous thrombosis and the escape of fluid into the cellular tissues which cause the severe local oedema reported by Shohl. Oral administration is also attended by difficulties; the hydrolysate has a nauseating odour and taste and may actually cause diarrhoea if the concentration of salts, especially sulphates in the powder, is too great. It may be found to be more convenient and equally effective to add methionine and cystine and possibly certain other amino-acids to the usual feeds, but trials are still too few for any conclusion to be formed.

PROPHYLAXIS

Active immunization

Diphtheria.—Alum precipitated toxoid with an Lf of 50 units per cubic centimetre in doses of 0·2 and 0·5 cubic centimetre at an interval of 4 weeks remains the favourite antigen; in sensitized subjects giving a sharp local or general reaction, almost all of whom are adults, toxoid-antitoxin floccules should be substituted for the second injection. Inoculation should be begun by the ninth month of life.

Whooping cough.—The early onset of whooping cough and the high fatality rate make it advisable to start inoculation earlier. Sako and his colleagues pointed out that half the number of children who die from whooping cough do so in the first six months of life and he recommended immunization between the second and third months; with three 4-weekly injections, 0·2, 0·3 and 0·5 cubic centimetre of an alum precipitated pertussis vaccine containing 40,000 million organisms per cubic centimetre, they found that 63 per cent of those injected gave indications of immunological response two years later. A follow-up study showed that of 1,904 individuals inoculated only 30 contracted mild whooping cough without fatality, as compared with 122 typical attacks and 13 deaths amongst 1,965 patients of similar age and circumstances except that they had not been inoculated. Were pertussis prophylaxis practised more widely infants would not be exposed so often or so early to risk of infection, making postponement to the age of 9 months tolerably safe. Furthermore, this prophylaxis could be safely and conveniently combined with diphtheria inoculations; the immunological response to each antigen is thereby enhanced in most cases.

Measles.—No further reports of measles immunization with egg-passage attenuated virus have appeared since Rake in 1943 summarized inoculations to that date, when of 1,281 children inoculated only two-thirds were available for the follow-up which showed that 450 (54 per cent) gave positive evidence of modified attack. (See Medical Progress (Critical Surveys section) 1945, p. 41.)

Bacillary dysentery.—In a review of the present position regarding the prophylactic and therapeutic efficiency of bacteriophage in Flexner and Shiga dysentery, Morton and Engley concluded that there was convincing proof of such action in experimental animals and they considered the time to be ripe for large-scale field trials. Boyd and Portnoy had reported on the employment of a German polyvalent bacteriophage preparation in North Africa amongst prisoners of war, in doses of 10 cubic centimetres swallowed before breakfast on three successive mornings; they observed no difference between the treated and the controls as regards prevention of attack, speed of recovery or rate of elimination of organisms.

Typhus.—Credit for the virtual absence of typhus in the North African and Italian campaigns, at a time when the disease was rife amongst civilians, is perhaps equally divided between immunization with rickettsial vaccines, Cox's egg vaccine for American troops and Craigie's modification for British troops, and disinfection by means of dichlorodiphenyl-trichlorethane (D.D.T.). Application of the powder to fully dressed persons is readily carried out by means of a blower and the treatment remains effective for weeks. Scrub typhus transmitted by rat mites can also be controlled by rickettsial inoculation but butyl phthalate was found to be more effective than was D.D.T. in disinfection (Lewthwaite).

Passive immunization

Measles.—The preparation of stable solutions of γ -globulin of uniform potency

has greatly altered measles prophylaxis, making it feasible deliberately to expose suitable susceptibles in order to confer the benefits of attenuation of attack—a procedure thought to be too dangerous with convalescent serum since potency was variable and deterioration through ageing was frequent, at least until desiccation had been introduced. Reports on the employment of immune globulin (Ordman, Jennings and Janeway, Stokes, Maris and Gellis) indicate that the protective dose is 0.1 cubic centimetre per pound of body weight given between the third and the fifth day after exposure to infection, some modification was obtained by reducing the protective dose to one quarter. It is more usual to halve the protective dose when attenuation is the aim. The latter team also obtained some therapeutic effect in pre-eruptive measles by using doses ranging from 5 to 35 cubic centimetres for ages from 10 months to 35 years. A more clear cut effect might be expected if the globulin were safe to administer intravenously. Greenberg, Frant and Rutstein found the globulin to be more than twice as potent as placental extract and re-affirmed the necessity of adjusting the dosage to age or to body weight. Globulin is moreover relatively free from systemic and local reactions which are common with placental derivatives, to which a death has recently been attributed (Answers to Queries)

Non-specific

The subject of cross infection in hospitals and its prevention has rivalled penicillin in the attention it has received in the medical press during the war years. The interference with normal methods of ventilation caused by blackout requirements, the dispersal of skilled nursing staffs, and to a less extent of medical staffs, and the constant and increasing shortage of domestic workers were the main factors favouring a higher incidence of cross infection than in pre-war years. In a recent review Mitman was unable to find positive evidence that any of the numerous preventive measures suggested, which were almost entirely based on experimental observations, were practicable or constituted an advance on the well tried measure of removing the infectious patient from his environment. A possible exception was ultra-violet irradiation, but dust seriously interfered with its efficiency. Although there are no grounds for complacency it is believed that the provision of adequate isolation facilities for infectious and potentially infectious cases and reduction in the size of hospital wards (preferably to four patients), with universal observance of the recognized rules of isolation nursing, should satisfy most requirements. Air conditioning plants should be incorporated in new units but the technical difficulties and the expense of installation in existing hospital wards are likely to be prohibitive.

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MENTAL DISEASES

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Contributions that have appeared in the literature in the last few years have been principally concerned with methods of treatment, although a few have dealt with general aetiological factors and with diagnostic methods. The social aspects of psychiatry have appeared in articles relating not only to war psychiatry but also to industrial psychiatry.

PRODROMAL CHARACTERISTICS IN PSYCHOSIS

These have been studied in 434 psychiatric patients under twenty-five years of age by referring to the records of the Child Study Bureau of the Chicago Board of Education. More than 5 per cent of the schizophrenic patients when examined in childhood had been described in terms of the 'shut in' personality. This study fitted the concept of process schizophrenia as distinct from schizophreniform episodes.

ENDOCRINOLOGY

The practical applications to psychiatry of endocrinological knowledge which is now available are still rather limited. A contribution of major theoretical importance has been made by Hemphill and by Hemphill, Reiss and Taylor. They describe a special form of atrophy involving chiefly the testicular tubules and their contents in schizophrenia. This change is characterized by hyalinization of the basement membrane, impairment of spermatogenesis, progressive degeneration of epithelial elements and final disruption of the tubule. The material was obtained by biopsy and so some of the criticism levelled at Mott's earlier work in the same field is avoided. The defect described is considered to be characteristic of a condition of chronic deteriorated schizophrenia and of catatonic schizophrenia. An important point which may be of practical diagnostic use is that although the highest degree of degeneration of the tubules may be present in the early stages, the patient may sometimes recover. Nevertheless these findings suggest that a high degree of atrophy portends, as a rule, an unfavourable outcome. Testicular biopsy may serve in some cases as a diagnostic and prognostic measure. No relation was found to the output of the 17-ketosteroids or to interstitial change. Important clues may thus be provided to the aetiology of certain types of schizophrenia. The authors suggest that the change is but one aspect of a general physiological abnormality.

DIAGNOSIS

Electroencephalography in obsessional neurosis

In twenty (64 per cent) of thirty one cases of obsessional neurosis the patients were considered to be abnormal, of these fourteen showed compulsive type patterns of wave, either with or without hyperventilation. A few of the patients presented actual epileptiform symptoms in the form of 'absences' (Pacella, Polatin and Nagler).

Electroencephalography in criminals

Silverman¹ concludes that the electroencephalogram cannot be considered to be a significant aid in the diagnosis of the source of criminalism. Excluding psychopaths from the criminal group, the percentage of electroencephalographic abnormality was about the same for normal criminals as for normal civil controls.

TREATMENT OF MENTAL DISEASE

Insulin treatment

A comparison of the results of the treatment of schizophrenia prior to the advent of insulin shock treatment with its results during the seven years in which insulin has been used, is made by Bond and Rivers. Of the groups treated by insulin shock 41 per cent of twenty-two patients maintained their status of recovery or of much improvement at the end of five years. The control patients showed only a 16 per cent recovery rate after the same period of time.

With regard to the alleged common occurrence of "relapse" after insulin treatment, the authors point out that this must be due partly to the larger number of patients for whom some period of health was gained. Insulin-treated patients enjoyed 251 years of health out of the possible 564 years comprising the collective follow-up periods, whereas in the controls only seventy-eight years of health were registered out of a possible 551.

Electrical convulsion therapy

This method continues to be widely used. Its application is most satisfactory in involuntal depressions of middle age and in depressions at earlier ages. Its usefulness is much less in certain cases of schizophrenia in which the deep insulin method is considered by some to be superior, at any rate in shortening the duration of recoverable attacks and in improving the quality of recovery. The method has been shown to be successful in a number of cases of involuntal melancholia after complete failure with previous oestrogenic treatment (Bennett and Wilbur).

Chronic hallucinosis has been treated by electrical convulsion therapy with some success. For example in one case the patient completely stopped hearing the hallucinatory voices after five treatments.

Kalinowsky emphasizes the necessity for producing convulsions in order to achieve the desired therapeutic effect. If the first stimulus does not lead to immediate convulsion a second stimulus with higher voltage should be applied forthwith. The application of several stimuli one after the other has no untoward effect, and the strength of the convulsion is not increased. Kalinowsky advocates early and adequate treatment in schizophrenia (twenty or more applications).

Recently a combination of pyrexial therapy and electrical convulsion therapy has been used in twenty schizophrenic patients who have proved refractory to all other methods of treatment. Intramuscular injections of 2-5 cubic centimetres of Sulfal (an aqueous suspension of colloidal sulphur, 1 in 100) induced a temperature of 39-40° C. (102.2-104° F.) and the electrical convulsion treatment was given during the pyrexial period. In seven of the twenty cases remissions, which seemed to be stable, were obtained (Fuster).

Electronarcosis

It is claimed that electronarcosis is superior to electrical convulsion therapy and is similar to insulin in its effects on schizophrenic patients. The principal difference in the effects of electronarcosis is the prolongation of the stimulation of the autonomic nervous system and the presence of other phenomena not observed in electrical convulsion therapy (prolonged flexor tone and forced gasping) (Thompson and his colleagues).

Curare in shock therapy

Curare in the form of Intocostrin has been used to "soften" the convulsion in pathological skeletal conditions, including fracture of the right femur at the surgical neck, compression fracture of the body of the vertebra, generalized osteoporosis and cervical osteoarthritis. No further skeletal damage was produced. The sometimes alarming effects on the respiration resulting from the use of curare were treated by the prompt administration of Prostigmin methylsulphate (1 in 2,000) intravenously, and artificial respiration was started as soon as possible. It has to be noted that the respiratory depression resulting from the use of curare may be delayed in its appearance and therefore the patient should be watched for twenty minutes after the drug has been administered. When there is any suspicion of myasthenia gravis the Bennett test is recommended (Bennett and Cash; Gottesfeld, Novaes and Fourzan).

Continuous narcosis

Continuous narcosis for four days has been used in the treatment of operational fatigue (so called) in air crews (Hastings, Glueck and Wright). The procedure reveals great technical ability to obviate dangers of collapse. It is, however, doubtful whether the application of this method would enable a higher percentage of individuals to go back satisfactorily to operational flying duties than would be the case when simpler methods are used.

Narco-analysis

Barbiturates—Intravenous injections of a barbiturate, usually sodium Amytal, were used considerably during the recent war for the treatment of psychoneurotic symptoms. The method can be used as a means of rapidly obtaining a history, and as a means of abreacting emotional experiences which have been repressed or which are at any rate too painful to recall in the ordinary state of full consciousness. It is doubtful whether the method has much justification other than the saving of time (Parfitt and Gall). All authors at least agree that the procedure must be combined with other methods of psychotherapy and with occupational therapy, and that there must be an adequate attendant staff at night time, and good nursing (Grinker and Spiegel).

Treatment of hysteria by intravenous administration of a barbiturate, and by verbal hypnosis and ordinary psychiatric therapy showed there to be no significant difference between the effects produced in a group treated with intravenous barbiturate and in those treated by the other methods (Lambert and Rees). The advantage of the use of barbiturates appears to be a saving of time, particularly in the case of hysterical amnesia. The method is of little value in treating somatic pains.

Nitrous oxide—Rogerson describes how he has used a Minnitt gas and air apparatus to introduce a twilight state which he has found useful for suggestive abreaction and the recall of repressed memories. It presents advantages over the more usual intravenous barbiturate method of narco-analysis in that it is safe and can be repeated several times in the same session. The patient's grip of the tube relaxes automatically with impaired consciousness, and inhalation of gas ceases.

Treatment of Korsakow's psychoses with vitamin B₆

It is claimed that recovery of the patient was hastened in a case of Korsakow's psychosis by the use of pyridoxin hydrochloride, with thiamine (aneurine) hydrochloride and mixed vitamin given orally. Pyridoxin hydrochloride was given into the subarachnoidal space by lumbar puncture, the pyridoxin being dissolved in the escaping cerebrospinal fluid and then being re-injected.

Amphetamine in acute alcoholism

It is claimed that the judicious use of Benzedrine (amphetamine) facilitates withdrawal from alcoholism in chronic alcoholics who have indulged in actual drinking bouts. Varying degrees of euphoria, instead of the usual sense of guilt and inferiority, were observed. All the patients were considered to be more receptive to psychotherapy and to social readjustment (Miller).

Treatment with endocrine substances

Involutional psychosis—Claims that hormone therapy is useful in involutional psychoses have been made, and have been repudiated. It is pointed out that although the percentage of recovery may not be increased, the rate of recovery appears to be so (Danziger, Schroeder and Ungar). The percentage of recoveries after three months or less was nearly four times as great as was the generally reported recovery rate in the same period. The authors emphasize that results may be expected only if the psychosis is clearly related to the climacteric.

Pituitary cachexia—A case of pituitary cachexia in a woman 41 years of age has been successfully treated with corticotrophic hormone. The emotional symptoms were hypochondriacal, and physically the patient was weak, thin and frail looking, with a "desiccated" sallow skin, the hair was brittle and scanty and the secondary sexual characteristics were atrophied (Hemphill and Reiss, O'Donovan). Corticotrophic hormone was given first for twenty four days in doses of 40 units, and a second course of fourteen injections of 25 units was given two months later.

OBSERVATIONS ON OTHER CONDITIONS

Industrial psychiatry

Selling states that in Detroit from a seventh to an eighth of the number of all the workers in industrial plants in which there are thousands of employees, accounts for nearly 100 per cent of all the accidents. There is a connexion between absenteeism, frequent changes of job, and accidents; the author regards all these as expressions of protest. An analysis of those who are prone to accident shows there to be six general factors as follows.

- (1) Physical inadequacy
- (2) Psychophysical inadequacy, in the sense of slowness in the carrying out of certain tasks, the slowness not being so marked as to be obvious and yet sufficient to produce strain and fatigue
- (3) Mental illness and mental defect
- (4) Preoccupation with other problems, especially domestic ones
- (5) Attitude towards superiors
- (6) A bad safety attitude, including indifference and antagonism to law and order

This analysis indicates some of the principles of prophylaxis which will be necessary in the post-war period. Ling analyses the role of bad working conditions and vocational misemployment in precipitating nervous breakdowns, and stresses the need for psychiatric advice at the Ministry of Labour. Burlingame, who became an industrial psychologist in 1915, and later a personnel manager, suggests that it is the man's own emotional drive that determines his real success from his own standpoint. Therefore, Burlingame says, the real problem is to make the man feel as important as he really is by making him as important as he is capable of being. An industrial psychiatrist must remain a doctor, retaining his personal independence and being only secondly an officer of the company. (It is difficult to see how this can be arranged unless the doctor is employed not by the company but by some other agency.) According to Burlingame, the psychiatrist must not appear to be a kind of policeman but must be a protector of the workers' interests. While the doctor should have a psychiatric point of view, he should appear as an industrial doctor and not as a psychiatrist, because a workman is apt to shy away from the latter. The author is against paternalism in industry, and believes that the patients' emotional problems should be dealt with through an employment bureau. If, however, the emotional problem is related to the job, the psychiatrist may invite the cooperation of the management in finding a cure. It is essential that the worker should feel himself to be part of the team in the total effort of industry. Industry must therefore continue to have in peace what it had in war—a goal which the worker himself is interested in reaching.

Child psychiatry

The effect of the absence of the usual family pattern in children's development has been studied by Freud and Burlingham. In certain respects such as health, hygiene, the development of skills and social response to other children, children in well run residential nurseries showed an advantage over children who led an ordinary family life. The former are at a disadvantage, however, in spheres in which the emotional ties are involved, such as those of speech and habit training. The absence of any possible father substitute in schools is regarded as a grave defect, since from the second year of life the child's relation to his father is of great importance in the satisfactory development of character and personality.

War psychiatry

The mass of work done in preventive psychiatry—especially in selection—during the recent war has not yet been published. One of the relatively few publications on the topic of selection claims that a battery of psychomotor tests gives some indication of the degree of efficiency necessary in pilots (Melton). Such tests tend to fail to allow sufficiently for the temperamental factor which is so important in operational flying.

Psychiatric selection—that is selection which takes account especially of the temperamental aspects—has its limitations, as Farrell and Appel point out. A careful study in one combat area showed there to be a higher rate of incidence of psychiatric cases among veteran troops from whom months of fighting had weeded out the weaklings than there was among inexperienced fresh troops. Selection cannot diminish the amount of breakdowns occurring among normal men. The rate of casualties rose in proportion to the length of service. Motivation, morale and leadership were all

important factors. In the man with a personal conviction of the necessity of fighting the war there was less likely to develop a psychoneurosis than in one who was indifferent or who was more concerned with purely local situations. Treatment for the men was regarded as a medical emergency, and was carried out as near as possible to the site of onset of the mental disturbance. Hospital inpatient treatment was regarded as a last resort, the patients were treated in a military atmosphere, under strict discipline.

In cases in which abreaction of the traumatic experience by means of barbiturate narcosis or by hypnosis had failed to remove the patient's symptoms, ergotamine tartrate, given first in a dose of 3 milligrams and then in doses of 2 milligrams every three hours for ten days, according to Heath and Powdermaker was found to be more useful in alleviating the symptoms than were parasympatheticomimetic drugs.

Psychological breakdown in the Navy

The study of psychological breakdown in the Navy has shown that there are two groups of exogenous factors which are not directly connected with the hazard of war (1) the conditions and type of service, including reactions to authority, disappointment over promotion and so forth and (2) domestic difficulties. The latter caused the more harmful and intractable reactions and in a large proportion of cases led to the men's being invalided. Analyses of the types of domestic trouble showed that infidelity of the wife or the *fiancée* headed the list, and that illness or death of relatives came second (Tooth).

The vocational aspects of neurosis in soldiers

This was studied by Lewis and Goodyear. The patients were posted to jobs chosen for them on the basis of the psychiatric opinion expressed on the training instructor's report. By this method the rate of return to military duties appeared to be raised from 36 per cent to 58 per cent.

Warfare in tropical conditions

Warfare under tropical conditions created several problems. Both climatic and social conditions favour the development of illness and there is lowered resistance to disease, mental energy is also sapped. As regards the social *milieu*, low moral standards prevail, especially in relation to sex and alcohol. Korsakow's syndrome and delirium tremens are considered to be especially common in the Tropics (McCartney).

Hyperventilation syndrome

A sense of apprehension, loss of consciousness, dizziness and tingling numbness of the extremities and face are characteristic of this syndrome. In civil life the syndrome has previously been encountered in emotionally unstable persons. Rushmer and Bond have recorded its presence in the airman, and they believe it is commoner than it is usually acknowledged to be. In emotionally stable airmen in whom the symptoms develop only under considerable stress, explanation and reassurance may be all that is necessary. In the case of others in whom the syndrome proves to be a pointer to general emotional instability, military reclassification may be necessary.

Effort syndrome (neurocirculatory asthenia)

A transient inversion of the T wave has been reported in two cases of "neurocirculatory asthenia" (Merrett). The ballistocardiograph, which gives a record of the forces generated by the recoil of the heart, is used in differentiating between individuals liable to neurocirculatory asthenia or with objective evidence of abnormality and those without such evidence to confirm their complaints. The instrument is considered to be useful in detecting malingerers (Starr).

The encephalogram

The encephalogram has been found to be of special value in diagnosis in three groups of pilots: (1) those with epilepsy, (2) those with psychoneurosis when organic brain disease has to be ruled out and (3) those with post-traumatic head syndromes when objective evidence is lacking (Silverman²).

Prefrontal leucotomy

Freeman and Watts, who have had more personal experience in the use of prefrontal leucotomy than have any other individuals in the English-speaking countries, have summarized the results so far. They give their estimate of results in terms of relief of symptoms and subsequent social adaptability. They do not consider the operation to be a success, even if the patient is satisfied, unless he adapts himself well to society. For example, a sufferer from anxiety neurosis, even although able to maintain his employment after operation, is considered to show a mediocre result if his behaviour is too distressing to his relatives.

The authors give the following table of results obtained by prefrontal leucotomy, excluding 34 recent cases.

DISEASE	NUMBER OF CASES	RESULTS PER CENT			DEATHS PER CENT	
		GOOD	FAIR	POOR	OPERATIVE	SUBSEQUENT
Involucional depressions -	- 77	67	21	8	4	11
Schizophrenias -	- 45	64	15	19	2	2
Obsessive tension states -	- 31	71	23	6	-	3
Psychoneuroses -	- 10	60	20	20	-	-
Undifferentiated (schizoid) -	- 7	14	43	43	-	14
Totals	170	65	21	12	2	7

The most striking neuropathological change after the operation is the severe degeneration of the nucleus medialis dorsalis of the thalamus.

Problems of ageing

The problems of ageing have been receiving increasing attention. Post concludes that factors other than physiological and anatomical ones are responsible for the origin of senile and arteriosclerotic mental disorders; constitutional factors must have been present in the patients, who previously had frequently shown a tendency to mental abnormalities. He suggests that mental hygiene in early life can offer some help in the prevention of mental illness in old age.

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OPHTHALMOLOGY

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LESSONS FROM WAR SURGERY

During World War I injuries to the eye had a poor prognosis. Retained foreign bodies were usually magnetic and responded to magnet-extraction instruments; the end results were nevertheless not good, and for this, infection was held to be responsible. During World War II the problem of infection, owing to the advent of the sulphonamides, has not been so formidable, yet war injuries are still a grave difficulty, for in contrast to the intra-ocular foreign bodies seen during the first world war, those derived from more modern explosives are mainly non-magnetic. The most significant issue arising out of the present era is therefore the removal of the non-magnetic intra-ocular foreign body. This has proved to be no simple task. Present-day missiles are largely made of aluminium—a metal used previously only rarely for this purpose. The little experience that had been gained in dealing with intra-ocular foreign bodies made of aluminium suggested that such retained foreign bodies were to a large extent innocuous. Unfortunately this is not the case. The experimental studies and clinical observations recorded by Savin^{1,2} show that whilst aluminium is not so destructive to the eye as are copper and iron, it nevertheless produces lesions in both the ciliary body and the retina. Such lesions are sufficiently extensive to justify the removal of these foreign bodies, were they easily removable. In practice, although successful extraction has been reported by the use of specially constructed snares introduced through a trans-scleral incision, the operation generally amounts to a formidable assault on the eye, and the results have not been encouraging; so much is this the case that the wisest course appears to be to abstain from operation except as a last resort.

The removal of the non-magnetic foreign body is likely to become a problem of major significance in the coming years, for it is anticipated that aluminium and non-magnetic alloys may be used to an increasing extent in processes in which magnetic substances were employed previously. More active measures against the prevention of industrial eye injuries, as well as the development of more refined methods for the localization of intra-ocular foreign bodies and of better techniques for their removal, are problems that press for attention.

Experiments in the use of organic and biological plastics as substitutes for scleral and corneal sutures (Blaine, Dollar and Sorsby) have advanced sufficiently to justify clinical trials. Such plastics are likely to find a special place in the treatment of scleral and corneoscleral wounds in civil life (Dollar).

THE CONTROL OF OCULAR INFECTION

Experimental studies

In contrast to the ease with which infection of the interior of the eye can be induced in the experimental animal is the extreme difficulty of obtaining infection in the outer eye. It has proved to be easy to establish the validity of the new chemotherapeutic agents in experimental infections of the anterior chamber, and to a lesser extent of the vitreous body, but in infections of the outer eye there is no valid experimental evidence by which to assess the efficacy and relative value of chemotherapeutic agents and to lay down criteria for their optimum use.

Most of the common organisms such as *Staphylococcus aureus*, *Streptococcus pyogenes* (*haemolyticus*, β_1) and pneumococcus, readily produce a purulent reaction when they are injected into the anterior chamber or the vitreous body; when the infection is sufficiently severe the process goes on relentlessly to the destruction of the globe. In contrast, the use of these organisms, as of the gonococcus, in attempts to produce

a purulent conjunctivitis or destructive keratitis by gross infection of the conjunctiva and of the scarified cornea, is uniformly unsuccessful. In these tissues there is nothing beyond a transitory reaction and the end result is spontaneous healing with little or no corneal damage. The one experimental infection that consistently gives a severe destructive lesion of the cornea is that due to *Pseudomonas aeruginosa*, unfortunately this organism is completely—or almost completely—insensitive to the new chemotherapeutic agents, and is therefore unsuitable in experimental studies in chemotherapy. The claim by Robson and Scott that standard experimental lesions can be obtained by the subepithelial injection of *Staph aureus*, streptococci and pneumococci has not been substantiated by another group of observers (Cole, Paterson and Sorsby).

As regards infections of the anterior chamber by organisms responsive to the sulphonamides, most observers agree that the general administration of sulphonamides checks these, infections of the vitreous show no such ready response, although the sulphonamides reach it in adequate therapeutic concentration.

The sulphonamides

Local use—Although soluble sulphonamides are used widely as local applications in the treatment of external infections of the eye, there is no valid clinical or experimental evidence to justify this practice. It has already been pointed out that there are at present insuperable difficulties in establishing standard experimental lesions of the outer eye. On the clinical side the failure of locally applied sulphonamides to influence the course of ophthalmia neonatorum must be regarded as incontrovertible evidence against their efficacy. Moreover, there is considerable theoretical objection to the local use of the sulphonamides. It is now established that pus inactivates sulphonamides, and of late the use of these substances in the form of local applications has declined considerably in popularity. The inefficacy of the sulphonamides when they are so applied has been emphasized by the striking results obtained by local penicillin therapy, and it is likely that before long it will be generally accepted that the local use of sulphonamides has no place in the treatment of the external infections of the eye. One important exception must, however, be made: the results obtained by local application of sulphonamides in trachoma, and in at least some cases of dendritic ulcer of the cornea, suggest that local therapy is very effective in some virus infections. It should be noted that both these virus infections are non-pyogenic in character.

Such experimental evidence as is available indicates that the sulphonamides employed locally do not control infection of the anterior chamber or of the vitreous (Klein and Sorsby, von Sallmann, Meyer and Di Grandi). The isolated clinical case of sulphonamide, must be taken with some reserve.

General sulphonamide treatment—The value of general sulphonamide treatment in infections of the anterior chamber has been repeatedly confirmed, both experimentally and clinically. General sulphonamide treatment has, in fact, become the main routine measure in postoperative infection of the anterior chamber, but the experimental and clinical results in infections that have spread to the vitreous are distinctly less satisfactory. In infections of the outer eye the sulphonamides have proved to be invaluable, they have revolutionized the treatment of ophthalmia neonatorum and should prove to be of immense help in combating the purulent conjunctivides seen in epidemic form in the Near East, the Middle East and elsewhere. The sulphonamides have, however, proved to be ineffective in acute choroiditis and in many cases of iritis, whereas in hypopyon ulcers they have given gratifying as well as distinctly disappointing results. In the treatment of trachoma general sulphonamide therapy clearly has a place, which, however, it is likely to yield to local sulphonamide therapy. In brief the sulphonamides represent the most striking advance for many years in the treatment of the external infections of the eye due to sulphonamide-susceptible organisms—and in practice this means most organisms commonly encountered.

Penicillin

Unlike the sulphonamides, penicillin remains effective in the presence of pus. It therefore has possibilities as a local therapeutic agent for purulent infections both of the outer and of the inner eye. The value of penicillin in infections of the outer

eye cannot be assessed experimentally for the reason already indicated (p. 59), but there is adequate experimental evidence that the introduction of penicillin into the anterior chamber and the vitreous body controls experimental lesions (von Sallmann; Leopold). Clinically the results obtained with penicillin therapy as a local application in the external infections have been very striking indeed. Whereas the sulphonamides reduced the course of ophthalmia neonatorum from a number of weeks to as many days, penicillin has reduced it from a number of days to as many hours (Sorsby¹). Adequate concentration of the drops used is essential because results are erratic with concentrations of less than 2,500 units per cubic centimetre; no less essential is the frequent application of drops, the best results being obtained with the instillation of penicillin at intervals of five minutes. In blepharitis the results are also most gratifying when penicillin is used as a local paint in a concentration of 1,000 units per cubic centimetre applied three times daily. Satisfactory results have been obtained in hypopyon ulcer (Juler and Young) but there is as yet no substantial information concerning the value of penicillin in purulent conjunctivitis of adults. It is likely that the outer infections of the eye, which have responded so well to general sulphonamide treatment, will respond even better to local penicillin therapy.

The fundamental difficulty in the use of penicillin for infections of the inner eye appears to lie in the fact that penicillin does not pass the blood-aqueous barrier. In both the experimental animal (Struble and Bellows) and in man (Rycroft) penicillin after intramuscular or intravenous injection of clinical doses, cannot be detected in any distinct quantity in the eye. On the other hand the diffusion of penicillin from the conjunctival sac into the anterior chamber and the deeper regions of the eye is also negligible. Rather better diffusion is obtained from subconjunctival injections of 1,000 or 2,500 units and from corneal baths; the introduction of penicillin directly into the anterior chamber presents technical difficulties, and there is evidence that any massive injection of penicillin into the vitreous is not free from deleterious effects (von Sallmann; Sorsby²). Several case reports on the use of penicillin locally in the anterior chamber, or by irrigation, indicate the value of this procedure, but there is as yet no clinical report on the value of penicillin applied locally in cases of vitreous infection.

Subject to further experience it would appear that general penicillin therapy is not likely to have any extensive place in the treatment of infections of the eye, or that the local use of penicillin will replace general sulphonamide therapy for intra-ocular infections. Local penicillin therapy may, however, prove to be effective over a wider range of conditions than general sulphonamide therapy, for it is likely to be of considerable value in the treatment of hypopyon ulcers and in infections of the anterior chamber and of the vitreous body.

One outstanding lesson learned from the experience obtained with the sulphonamides and with penicillin is that a sharp distinction has to be drawn between infection of the eye and inflammation of the eye. The efficacy of the sulphonamides and of penicillin in infections stands out in marked contrast to their absolute or relative inefficacy in inflammations such as iritis and choroiditis. The gaining of fuller understanding of the nature of intra-ocular inflammation has become an urgent practical task.

VIRUS INFECTIONS

With the decline of epidemic outbreaks of kerato-conjunctivitis, interest in this particular infection has declined, but the studies on epidemic kerato-conjunctivitis have greatly stimulated investigations into virus infections of the eye generally. The clear recognition of a virus type of ophthalmia neonatorum susceptible to sulphonamide treatment, as well as the gratifying results in trachoma from such treatment, have added further interest to the study of the virus infections. It is now recognized that both the virus of trachoma and of inclusion blenorrhoea belong to the group of large sized viruses allied to those of lymphogranuloma inguinale and of rat pneumonitis, which have been shown to be susceptible to the sulphonamides. Inclusion blenorrhoea shows a purulent reaction, but none of the other known virus infections of the eye produce pus; when pus is present it is due to a secondary infection. The absence of the purulent discharge in virus infections generally—clearly brought out by the studies on epidemic kerato-conjunctivitis—have focused attention on the mass of corneal lesions in which no bacterial organisms can be found, and in which purulent discharge

is lacking. The presence of inflammatory reactions together with these negative features point to the possibility that a large and nondescript mass of corneal lesions is of virus origin—a supposition that has been prevalent for years but which still lacks confirmation. On theoretical grounds the whole group of proved or assumed herpes infections of the cornea should not respond to sulphonamide treatment, since the herpes virus belongs to the smallest viruses and there is no experimental evidence that these are affected by the sulphonamides. On the other hand satisfactory results can be obtained in at least some cases of dendritic ulcers by intensive local sulphonamide therapy, and there is much to be done to elucidate the clinical picture that passes under the name of dendritic ulcer. It is possible that this is not a uniform group, and that the herpes virus is not responsible for more than a fraction of these cases.

GENETIC ANOMALIES

In statistics on blindness, malformations, congenital anomalies and hereditary affections now occupy (collectively) the chief place among the causes of blindness in the blind population under fifty years of age. This has been brought about by the steady diminution of infective disease, and the present tendency is likely to become emphasized with the advent of the new chemotherapeutic agents. Interest is inevitably bound to be centred with increasing intensity on the group of lesions classified as maldevelopments and hereditary disease.

A clearer appreciation of hereditary corneal lesions has emerged during the last few years, and Buckler's classification of three types—dominant granular, dominant reticular and recessive nodular—has been amply confirmed by other observers (Mutch). It would appear, however, that the view expressed in this classification that the dominant varieties of corneal dystrophy are essentially mild lesions, is not altogether borne out by clinical experience.

In contrast to the three varieties and modes of inheritance of corneal dystrophy the mode of inheritance of glioma of the retina appears to be of a uniform type—monofactorial irregular dominance (Griffith and Sorsby), there is no reason to assume recessive inheritance in some cases, but the question still remains whether or not there is a non heritable type of glioma. The mass of sporadic cases may represent a different type of glioma, as is suggested by the finding that in the proved hereditary gliomata the incidence of bilateral affection is about 60 per cent as against that of 15–20 per cent in the sporadic cases. The finding that histologically the bilateral cases spring from both nuclear layers of the retina, and occasionally from the inner nuclear layer, whereas the unilateral cases spring from the outer nuclear layer only (Cumings and Sorsby) suggests that we may indeed be dealing with two distinct types of glioma.

The genetic aspects of glaucoma still require much detailed study. There is no incontestable evidence of a dominant type of buphthalmos, all the evidence points to a recessive mode of inheritance, but this too is a matter of doubt since a high rate of consanguinity has not been shown in these cases (Westerlund). In contrast, juvenile glaucoma is clearly inherited in a dominant manner, whereas the position as regards glaucoma in the elderly is distinctly obscure. Attempts to link buphthalmos, juvenile glaucoma and senile glaucoma together into a uniform group are not convincing. A fuller appreciation of the sub-varieties in each group will have to be achieved before the position can be cleared up.

TRANSMITTED MATERNAL INFECTIONS

Although the nature of congenital malformations and maldevelopments is still largely obscure, the recognition that there are anomalies due to transmitted maternal infections, as distinct from anomalies due to inheritance, is helping greatly to clarify the issue. No new principle is evolved in these procedures, since transmitted syphilis is the basis of a mass of congenital eye diseases which are seen in congenital syphilis. It is now clear that syphilis does not stand alone as a potent factor in fetal malformations. A fairly well defined type of central chorioiditis (toxoplasmic chorioid-retinitis) is now known to be caused by encephalozootic parasites which produce subclinical conditions in the mother, and are able to pass the placental barrier. Starting from an isolated and incomplete observation by Janku in 1924, American observers have now considerably clarified the picture although the diagnosis still relies on an unsatisfactory complement fixation test (Wagener). The finding

by Gregg in 1941 that German measles in the early months of pregnancy can induce ocular malformations in the offspring—an observation since amply supported by other observers—again emphasizes the part played by transmitted maternal infection. In this case a virus is responsible, and the ocular lesions range from cataract to extensive fundus degeneration. It is likely that other organisms capable of passing the placental barrier will be revealed and that the old and much abused concept of intra-uterine infection may assume a new validity.

MONOGRAPH PUBLICATIONS

A review of the year's work cannot but take note of three excellent monograph publications which appeared during the period under consideration. The literature on cataract has been greatly enriched by the exhaustive study by Bellows, and the first volume of Berliner's *Biomicroscopy of the Eye* represents a first adequate textbook in the English language on slit-lamp microscopy. Kuhn's *Industrial Ophthalmology* is a pioneer effort in a much neglected field of ophthalmic literature.

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ORTHOPAEDIC SURGERY

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The scope of orthopaedic surgery today is tremendous. As the President of the American Orthopaedic Association said recently in a presidential address, in surveying the literature of the last few years alone it is appalling to note the vast number and variety of subjects that are presented for our study. In a lifetime none of us could presume to attempt mastery of them all. The President suggests, indeed, that various specialties will develop within orthopaedic surgery as they have developed in general surgery.

Much has been written in recent years, as is natural, on war surgery and on the manner in which orthopaedic practice has been directly modified by war experience. As might be expected, the chief subjects dealt with have been wounds and their complications, foreign bodies and their detection, amputations, and the care and rehabilitation of the wounded, and allied matters. It is clear that wounded men now have a much better chance of recovery than they had in any previous campaign. Many factors contribute to this happy result, particularly early surgical treatment in the forward areas, the easier transportation of the patient—attributable to early splinting—the use of tetanus toxoid, of penicillin and of the sulphonamides, and the prolific use at all stages of blood transfusion.

AMPUTATIONS

When amputation is delayed for from twelve to twenty-four hours, infection of the stump is almost inevitable and in such cases either a guillotine amputation or a flap amputation with flaps left widely open until sepsis has subsided, is carried out. A two-stage procedure is now suggested (Jack and Charnley). In the first stage a flap operation is done and after haemostasis is complete, sulphanilamide powder is dusted into the wound and a dry gauze pack is inserted well up into the folds of the flaps. The ends of the pack are left projecting, the flaps are pulled together over it by means of four or five sutures and a well padded dressing is applied. The second stage is undertaken four or five days later: the pack is removed, more sulphanilamide powder is applied, and the flaps are closely sutured without drainage. Whereas the guillotine operation seeks to side-track infection and the loose closure method to minimize its effect, the two stage method aims at and frequently succeeds in preventing infection.

According to Harris the principles governing the technique of amputations in the field are (1) the saving of as much of the limb as possible in order to permit the widest scope for the subsequent definitive operation, (2) treatment of the wound by the standard rules established for dealing with war wounds—debridement, removal of foreign bodies and dirt, open drainage, and chemotherapy, (3) when the infection has been controlled, the management of the resulting stump with its open wound in such a manner (by traction or secondary suture) that healing will occur quickly and with a minimum deformity of the stump.

After the wound caused by the field amputation has healed, the secondary or definitive operation can be undertaken. Since this is to provide as nearly perfect a stump as can be constructed, primary healing is an important requirement, the operation should be performed, therefore, only after the wound is soundly healed. The necessity for this second operation is to provide a stump which will function well when it is fitted with the best available prosthesis. The amputation is dependent upon the type of prosthesis most suitable for amputations at certain levels of the lower extremity. Just as there are four types of prosthesis, so are there four standard amputations to correspond to them. Syme's amputation is the most useful of all amputations of the lower extremity because of the perfection of its weight-bearing qualities. Any imperfections that may

occur in a Syme stump are due to errors of technique, which may arise in either the operative or the postoperative period.

Amputation stumps below the knee must be sufficiently long to move the artificial limbs into which they fit, but they need not be longer. There is no advantage and there are serious disadvantages in leaving a longer stump. The ideal stump below the knee is 5½–6 inches in length. When it is necessary to perform an amputation which sacrifices the function of the knee joint the Gritti-Stokes type gives a useful stump, but probably a mid-thigh amputation is best. Amputations higher up are less useful but they may be fitted and may give some degree of function.

FRACTURES

Much has been written in the last two years on what are known as fatigue fractures (Hartly; Ingersol), the earliest type of which was the march fracture of the metatarsal bones. These fractures occur in apparently normal bone without history of trauma, and are said to occur when the rest period is inadequate. They happen chiefly in early manhood but may also take place in childhood, and they have been recorded as having occurred in the tibia, the femur, the fibula, the calcaneum and the dorsal vertebrae. Rest, if necessary in plaster of Paris, is sufficient treatment, but return to weight-bearing is gradual. The significance of such fractures is threefold: (1) missed diagnosis may lead to recurrence or to involvement of the opposite side; (2) incorrect diagnosis may lead to surgical intervention for suspected infection; (3) the medico-legal aspect involves, among other things, medical discharge from the army, compensation and pension.

Fracture of the scaphoid bone

There is no difference of opinion on the treatment of the recent fracture because most surgeons agree that immobilization in a skin-tight plaster wristlet to include the first metacarpal bone is most likely to ensure union, although the time necessary until union occurs varies with the particular type of fracture and a successful result can be proved only by x-ray examination. In the case of the ununited fracture, however, opinion varies considerably. Non-union is common principally because of late diagnosis but also because the blood supply of the bone is such that interference is simple and frequent with a natural sequence of post-traumatic necrotic changes and difficulty in union. Even in favourable cases which have been diagnosed early, incomplete reduction and insufficiently prolonged immobilization may commonly cause non-union.

The methods of treatment of ununited fractures of the carpal scaphoid bone are as follows:

- (1) Prolonged immobilization.
- (2) Multiple drilling of the fragments.
- (3) Bone-pegging or grafting operations.
- (4) Excision of one or both fragments, or even of the proximal row of carpal bones.
- (5) Fusion of the scaphoid with the capitate and lunate.
- (6) Arthrodesis of the wrist.

There may be a place for many of these operations but it is likely that, whichever is used, the earlier the operation the better the result. The type of fracture and its age—and also, it may be, the surgeon—should be carefully considered. It is doubtful whether the complicated operation of grafting has any place in the treatment; removal of both fragments or of the larger one, especially if it is avascular, is of distinct value, but in cases in which there is already some degree of osteoarthritis the procedure of fusion of the wrist is indicated. It is interesting, however, to read of the latest development in treatment of these troublesome cases. Waugh and Reuling favour excision and replacement of the scaphoid bone with a prosthesis. They have used a vitallium replica in three cases. When the fragments are removed they are assembled in order to judge the size and shape of the replica. This is inserted in place and after two weeks movements are started. No remarks are published on the end results obtained by the treatment.

Girdlestone reviewed the problem and advocated more common use of conservative measures; he gave a sound word of caution against the carrying out of elaborate

surgical procedures by less experienced operators who could achieve better results by simple non-operative means.

Fracture of the calcaneum

As a parallel to the surgical removal of the patella and the calcaneum at present is often carried out for comminuted fractures of these bones it is now suggested that a similar procedure is a sound method of treatment for a fractured calcaneum. The operation was described at a recent meeting of the Association of Surgeons and good results were claimed for it. This fracture still remains a puzzle and of the many different methods of treatment presented it is unlikely that one is better than another. The chief cause of disability is the damage to the talo-calcaneum joint and an arthrodesis of this joint is often carried out in either the immediate or the late stage. Armstrong secures the fixation by means of a tibial graft inserted through the neck of the talus into the calcaneum, the position being controlled by means of x-ray examination.

GROWTH AND HEALING OF BONE

Some interesting observations on the growth and healing of bone have recently been published. Many people believe that 90 per cent of non-union of bone is preventable and that it is caused chiefly by too active treatment or rather by 'meddlesomeness'. Once the fragments are put in position they should be left alone. The phosphatase content of the fracture haematoma seems to bear some relationship to union. In the presence of infection this content is decreased and healing is delayed. Materials which depress phosphatase activity should not be used as internal splints—stainless steel and certain plastics do not have this effect. Some investigators have found that the injection of procaine hydrochloride into the fracture increases the rate of callus production. Mowlem has reported excellent results in various fractures from the use of cancellous chip grafts for the restoration of contour and continuity. Apparently in using these cancellous grafts the accepted standards of bone grafting are reversed. Instead of the splinting of the defect with a dense almost non-cellular, transplant which may act in addition as a bridge for osteogenesis or as a poor source of new bone, other methods of fixation are used and the defect is filled with chips of cancellous bone—about 0.5 × 2 centimetres—obtained from the ilium, the survival of which will produce the required new bone within a matter of weeks. The cases reported on show that this new method is rewarded by increased operative simplicity, by a greater number of postoperative recoveries, by added certainty of results and in the reviewer's experience, by more rapid union (Bell, Leading Article).

The stiff joint after fracture gives more anxiety and often leaves serious disability. This is particularly the case when the knee joint is involved and although such a complication is to a great extent preventable it is in some cases inevitable. Bennet further in an ingenious operation in which much of the scarred tissue binding the quadriceps to the femur is excised along with the vastus intermedius, a muscle which also is usually one mass of scar tissue. No lengthening of the rectus is carried out and as a consequence return to function is quick if active movement is started at an early date.

Fractures in the region of the elbow joint are not uncommonly followed by limitation of extension of the joint. Slight limitation of under 30° is no appreciable handicap but greater degrees of limitation may give rise to serious occupational difficulties. The cause of the difficulty after fractures may be due to distortion of the joint surfaces, to malunion with bony projections or excessive callus formation, or to fibrous thickening and contracture of the capsular ligament. Wilson suggests a capsulectomy for relief of the last type. The operation is performed through an anterior incision passing between the brachioradialis and the brachialis although because of the possibility of keloid formation a medial incision may be used, especially when the patient is a child. Wilson reports good results but some of his patients had a temporary postoperative radial palsy.

When loss of forearm rotation is caused by one of the many pathological conditions of the inferior radio ulnar joint the movements can be restored by resection of the distal end of the ulna. This procedure is useful in certain cases of radial deviation of

the hand, a condition which may occur when a Colles's fracture has been incompletely reduced. It is a simple and successful operation (Boyd and Stone).

TRAUMATIC ISCHAEMIA

Degeneration of peripheral nerves

An interesting, almost new, condition is that of traumatic ischaemia of peripheral nerves. It is the result of some injury to the limb which is followed by gross swelling or other formidable signs of severe circulatory disturbance. Often there ensues disturbed function of the deep nerve trunks to the affected part, particularly sensation of the glove or stocking type. The motor loss is usually confined to the intrinsic muscles of the hand or foot. Muscular contractures of a mild degree result. Spontaneous recovery occurs in most cases, but is slow. The cause is thought to be a traumatic arterial spasm such as is now recognized to be the effective element in Volkman's ischaemia. Adams has shown that "all nerves receive a blood supply, and that it is derived from regional vessels which contribute, however, to the formation of a longitudinal vascular pathway along the nerve". The evidence suggests that it is unlikely that traumatic arterial spasm can by itself cause ischaemic degeneration of nerve trunks without at the same time producing necrosis in the muscles. The only way in which traumatic spasm could have such an effect would be by extension of the local arterial spasm to involve the regional vasa vasorum. It may also be that pressure beneath the unyielding deep fascia produces the effect on the nerve trunks. This is suggested from the history of gross swelling of the limb, the mode of onset of the anaesthesia, and the fact that those nerves lying outside the deep fascia at the level of the swelling often escape.

In many of the cases described by Parkes, peripheral degeneration of the nerve could have been prevented by early recognition of the condition and by appropriate surgical intervention designed to relieve the ischaemia. The early management includes such measures as the forcing of the collateral circulation by the raising of the body temperature. Heating of the unaffected limb while the affected limb is exposed to environmental temperature has been found to be especially valuable. Oxygen therapy, the injection of antispasmodics such as papaverine, and intrathecal injections of Novocain (procaine hydrochloride) have all been recommended, but in most cases early exploration of the artery with periarterial stripping and possibly arteriectomy is indicated. Induction of peripheral dilatation by sympathetic paralysis is also suggested. In cases of gross swelling, it is well worth while to relieve tension in the limb by free incision of the deep fascia even at the expense of converting a simple into a compound fracture, and indeed the wound may be left open in order to lessen the likelihood of obstruction of the circulation by oedema. Tight circular bandaging, with or without a plaster of Paris case, appears to be a particularly dangerous procedure.

PAINFUL CONDITIONS OF THE BACK AND SPINE

Prolapse of the intervertebral disc

Pains in the low back accompanied by a sciatic radiation are believed to be due in the vast majority of cases to a protrusion of the intervertebral disc (Dandy¹). The patient complains of a backache with pain shooting down the leg, usually after a relatively trivial injury such as may result from a lift, a bend or a strain. During the acute phase these pains are intensified by the act of coughing or sneezing. The only valuable objective finding is a diminution or loss of the ankle reflex. Many believe that this syndrome is so clear cut and so manifestly indicative of its origin that it is unnecessary to undertake further investigation, although Spurling, believing that only 60 per cent of cases can be so diagnosed, examines the remainder by injecting a contrast medium into the spinal canal in order to observe a filling defect in the myelogram so obtained. He uses Pantopaque which, although it is relatively harmless, he aspirates immediately (Spurling and Thompson). The disc or its prolapsed portion may be removed, without removal of bone, by means of an interlaminar approach. Many large series of satisfactory results have now been published.

Other articles provide renewed assurance that the time has not yet come when it is necessary to abandon all previous concepts about the back in favour of the intervertebral disc theory. Larminie, in an anatomical study, has shown that compression of the spinal nerve roots may be produced, *inter alia*, by posterior tipping of the vertebral bodies, anomalies of the first sacral body, narrowing of the intervertebral

in addition these depend upon the accuracy with which the foot is applied to the splint and upon its use until the child begins to walk. Bell and Grice describe several useful refinements in technique.

Soft-tissue injuries

Many sprains and other soft-tissue injuries are adequately treated by means of an ethyl chloride spray (McIntosh and Petrie). This succeeded the treatment of sprains by procaine hydrochloride injections as advocated by Leriche of Strasbourg. Use of the ethyl chloride spray is now advocated with the object of producing cutaneous anaesthesia and so encouraging active movement. The cases treated included those of sprained joints, traumatic synovitis and injuries to muscles and periarticular tissues, as well as a few cases of pain of indefinite origin.

Immersion foot

Immersion foot (Ungley and Blackwood; Critchley) is the name given to the very painful condition caused by prolonged exposure to wet and cold; it is now recognized as having been the cause of many casualties among those taking part in Arctic expeditions and among shipwrecked crews adrift in waterlogged lifeboats. In such conditions the feet become numb and swollen. Later, blisters, ulcers and gangrene are present. As the circulation is restored acute vasodilatation sets in, characterized by intense burning pain and objectively by oedema, redness, heat, distended veins over the feet, and hyperidrosis. Subungual haemorrhages and loss of nails may occur, and in severe cases there is loss of the toes or of the feet. In patients who recover and keep their feet a chronic sensory neuritis remains.

Much harm can be avoided by proper management when the sufferers are rescued. The patient should be carried and should not be allowed to stand or to walk. His tight boots, stockings and other coverings are cut off with extreme care. The top part of the body is warmed but the affected parts are exposed to the air and are kept cool. The application of hot water bottles, warmth and massage to the parts is disastrous and is to be avoided. The methods of treatment are rather refrigeration by gentle and loose application of ice bags, dry cooling with an electric fan, and mere exposure to the air at room temperature after elevation of the limb. Strict asepsis and gentle handling are important.

Infantile paralysis

Controversial reports have appeared recently about the Kenny method of treatment of infantile paralysis. The treatment was sponsored by various authorities in Australia where a number of clinics have been established to carry it out. It is somewhat remarkable in its concept. Although Miss Kenny accepts the usual idea of damage to the anterior horn cells and the presence of flaccid paralysis, she believes the main symptoms to be muscular spasm and incoordination and the loss of ability voluntarily to contract the muscles (described by her as "mental alienation"). In the case of foot drop it is suggested that the gastrocnemius is in spasm and that the dorsiflexor muscles are prevented from functioning by mental alienation. In the first phase of the treatment, spasm is treated by the application of hot packs while the patient is in a supine position supported by a footboard—not so much as a splint to maintain the normal standing reflexes. The second phase is that of muscle re-education—massage is never employed—which is not attempted until spasm is relieved. Probably the best part of the treatment is the muscle re-education, but this is no new idea. There is indeed as yet little ground for enthusiasm about the Kenny method.

REHABILITATION

A great deal of literature on rehabilitation has been published in recent years. Rehabilitation comprises the supervision and treatment of patients during the later stages of disease and disability, an aspect of treatment which hitherto has been the province of the general practitioner and a duty almost automatically performed by him. The whole problem has obtained such prominence in the lay press that it has now entered the realm of politics. Rehabilitation is, however, no new discovery. The patient is studied from the beginning of his illness and every effort is made to obtain the best possible result. He is no longer left to vegetate in bed but his general physical condition

is maintained while he is still in bed. Provided muscular contractions and relaxations are carried out systematically, the damaged structures do not suffer. Deterioration is reduced to the minimum so that when the in-patient eventually becomes an out-patient it is not necessary to begin a process of general reconditioning. At this stage it is desirable to substitute more active measures of increasing severity, such as resisted exercises by the weight and pulley method, which can be adapted for the graduated exercise of any muscle group. The most useful single exercise for the patient in bed is quadriceps drill: he is encouraged to contract and relax to the fullest extent his quadriceps group of muscles for five minutes of every wakeful hour of the day. By this means his legs are sufficiently strong when he gets up to allow him to walk almost at once.

There comes a time in the convalescent stage of all serious disease and disability when it must be estimated whether the patient will be able to return to his former employment, whether some modification of his original work will be necessary, or whether a new vocation must be found for him. "Rehabilitation," Howitt says, "presupposes that the medical profession must not restrict itself to the immediate cure of disease, but must also guide the general welfare of the community in the achievement and maintenance of health, in the selection and training for vocation and re vocation, and in the prevention and correction of disease and disability, equally as in their remedy. It is a social issue in which every Ministry is concerned, but in which, surely, medicine must take the lead."

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PAEDIATRICS

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Despite the years of war advances have been made in paediatrics. The treatment of appropriate infections with the sulphonamide group of drugs or with penicillin has helped considerably in the lowering of mortality in infancy and in childhood. Problems which presented themselves prior to the outbreak of war have been further elucidated during the last five years and some of these are worthy of review.

HAEMOLYTIC DISEASE OF THE NEWBORN

Haemolytic disease of the newborn (erythroblastosis fetalis) has been recognized for some years, but it is only recently that it has been closely studied (Annotation; Gimson; Mollison). The treatment of these cases has been facilitated by the fact that many hospitals are now able to test the blood of mothers and of infants for the Rh factor. The establishment of blood banks throughout the British Isles, as a wartime measure, has made supplies of Rh negative blood readily available at any time. Approximately 15 per cent of mothers are Rh negative; the majority of these, although mated with an Rh positive husband, give birth to normal healthy infants. In the course of time, an explanation of this fact will no doubt be forthcoming. How much of the damage to the infant takes place *in utero* is not clear; judged by clinical findings, some infants appear to be grossly damaged at birth; in others the haemolytic process is slow and, despite the giving of repeated transfusions of Rh negative blood, haemolysis continues for several weeks. Cases of sudden death are disconcertingly frequent, despite a high erythrocyte count and haemoglobin count. It would appear, therefore, that the treatment of this disease, as at present carried out, is not entirely satisfactory; in some cases exsanguination transfusion with Rh negative blood may be a partial solution of the difficulties. Each case of erythroblastosis fetalis should be kept under observation for some weeks before the infant can be considered to be out of danger.

The work of Yannet and Lieberman suggests that the after-effects of erythroblastosis may not be accessible for some years and in consequence a fascinating new field of research suggests itself. Snyder, Schonfeld and Offerman have confirmed the work of Yannet and Lieberman, and in the combined total of their cases there were 124 mental defectives of an undifferentiated type, twenty-two of whom were Rh positive and had Rh negative mothers. This fact is of statistical significance, since the number is twice that which one would expect in a random sample of the population. Parsons states that much cerebral damage probably occurs before the birth of the infant. We now await further observations on all cases of erythroblastosis fetalis in which the patients have survived for a number of years.

POLIOMYELITIS

Of recent years a new outlook on the mode of spread of poliomyelitis has been accepted. Formerly it was thought to be by droplet infection, the virus reaching the olfactory nerves and from there passing to the central nervous system. More recently the work of Sabin and Ward and of Toomey, Takacs and Tischer suggests that the virus is ingested and reaches the central nervous system from the alimentary tract. The virus may be isolated from the stools of children with poliomyelitis, from those of children convalescing from it or even from those of healthy children. It may be regularly obtained from the sewage of hospitals at which patients with poliomyelitis are being nursed. Flies have been shown to act as carriers of the virus. Trask, Paul and Melnick were able, by collecting flies from the surroundings of dwellings occupied by patients with poliomyelitis, to demonstrate the virus in the faeces of such flies or in the bodies of the

flies themselves. If flies were obtained from non-epidemic areas, the virus was not isolated. This suggests that food and drink may be infected from flies acting as carriers of the disease. It must therefore be concluded that prevention of spread of the disease could be brought about by improvement in sanitation and by the widespread use of an insecticide such as D D T.

FIBROCYSTIC DISEASE OF THE PANCREAS

Andersen gave the first comprehensive and convincing description of fibrocystic disease of the pancreas. She divided her cases into three groups, as follows. Group (1) comprised infants born at term, who died within one week with symptoms of intestinal obstruction. At necropsy inspissated meconium was found in the bowel and atresia of the bowel itself was not uncommon. The pancreas showed extensive fibrosis with formation of cysts. Group (2) consisted of infants who died between the ages of one week and six months. These were brought for treatment because of failure to gain, because the abdomen was large, because the stools were fatty or because of chronic infections of the respiratory tract. In some cases attention was focused primarily on the respiratory infection, in others the nutritional problem was stressed. In all cases the appetite was very good and the infant took an adequate diet very hungrily without apparent benefit. The stools in all cases were characteristically large and pale, with a foul, offensive, penetrating and acrid odour. At necropsy fibrosis and cyst formation in the pancreas due to occlusion of the small ducts was found in all cases. In addition a varying degree of pulmonary fibrosis with bronchiectasis and milary abscesses or bronchopneumonia was described. Group (3) included children of ages ranging between six months and fourteen and a half years, they came with the diagnosis and showing the signs of coeliac disease. The history however showed that the symptoms had existed from the first months of life and that from six months of age onward the stools became increasingly offensive, the children were underdeveloped, with large abdomens, flabby muscles and wasting in the gluteal region. They most frequently succumbed to respiratory infections—bronchitis, bronchopneumonia or bronchiectasis. The fat content of the stools was high, ranging from 40 to 60 per cent, the anorexia is a prominent symptom. An examination of the duodenal contents showed trypsin to be completely absent. At necropsy fibrosis of the acinar tissue was found, together with stenosis or atresia of the pancreatic ducts with consequent cyst formation. In many cases there was evidence in the lungs of purulent bronchopneumonia or bronchiectasis, or in the mucous membrane of the bronchioles there was a condition similar to that seen in vitamin A deficiency with squamous metaplasia of the superficial layers and keratinization.

It may be asked why, in the absence of pancreatic secretion, fat may still be split, as is shown on examination of the stool, Andersen suggests that this should be attributed to the lipase of the succus entericus. In her series of cases there was a history of other children in a family having suffered from similar symptoms. Deaths were reported in more than one child of a family in a proportion of these cases. This disease, fibrocystic disease of the pancreas, must therefore be looked upon as a familial one.

Andersen discusses the possible aetiological factors which would cause an obstruction of the smaller pancreatic ducts in fetal life in association with atresia or stenosis of other epithelium lined passages. The condition sometimes appears in several siblings of the same family. The author thought that the three following aetiological agents fulfilled these requirements: (1) congenital malformations, (2) inflammation of the pancreas during fetal life and (3) vitamin A deficiency during fetal life. Having discussed points for and against deficiency during fetal life, Andersen is inclined to think that vitamin A deficiency has the most convincing support. In the diagnosis of the disease during life, the most convincing single finding is absence of trypsin from the duodenal juice. Treatment at present comprises the administration of keratin coated tablets of pancreatin—from 60 to 120 grains per day—given with meals. The efficiency of this treatment has not yet been fully assessed (Blackfan and May).

THE PENICILLIN TREATMENT OF INFECTIONS IN INFANCY

Investigating a series of infants under the age of one year at the Hospital for Sick Children, Great Ormond Street, London, Bodian was struck by the high rate of

incidence of *Staphylococcus aureus* as a causative factor in their disease. The organism was recovered in 75 per cent of all the cases. In the neonatal period (up to the age of one month) its incidence was 81 per cent; in 25 cases in which a positive blood culture was obtained, *Staph. aureus* was isolated from the blood stream in 19 cases, i.e. in 76 per cent. The significance of these findings is more fully appreciated when one attempts treatment, since it is only by the parenteral administration of penicillin that the infection may be overcome.

So far as paediatrics is concerned, it would appear that penicillin has its greatest uses in the neonatal period, since the infant has apparently an extremely poor mechanism for defence against *Staph. aureus*. The dosage advocated by Bodian is 1,000 international units per pound of expected body weight, spread over the twenty-four hours. He found that given at four-hourly intervals (usually coinciding with feeding times) an adequate level of penicillin in the blood is maintained.

Positive blood cultures were obtained most often from newborn infants with umbilical infections, infected eyes and skin infections. Occasionally they were also obtained from infants with otitis media and mastoid disease; the response to the giving of penicillin in such cases was, on the whole, most satisfactory.

THE USES OF HUMAN BLOOD PLASMA IN PAEDIATRICS

After the outbreak of the recent war blood banks were established throughout the British Isles. These have made obtainable large quantities of plasma which has been preserved in a dried condition and is therefore readily available for use. Gunn, Pugh and others have recently reported on the benefits of intravenous plasma therapy in a variety of conditions. Perhaps its greatest use will be found in combating the acute dehydration accompanying severe diarrhoea and vomiting which is frequently referred to as gastro-enteritis. It is common knowledge that with Hartmann's solution or physiological saline, administered in either full or half strength, dehydration is rapidly made good but the amelioration cannot be maintained. These authors have found, however, that after preliminary hydration the administration of diluted plasma can be continued for a considerable period with great benefit and thus the tendency to dehydration can be checked.

It would appear that the giving of blood plasma should be looked upon as of great importance in the feeding of the infant as well as in the replacement of his depleted blood proteins.

Gunn stresses the fact that the plasma helps to make good deficiency in electrolytes and he gives the plasma in dilutions of one part of plasma to three or four parts of half-strength Hartmann's solution, to which from 2.5 to 5 per cent of glucose has been previously added. Both Gunn and Pugh are convinced of the efficacy of intravenous plasma therapy in lowering infant mortality from diarrhoeal diseases. In congenital pyloric stenosis, prematurity and severe coeliac disease marked lowering of the blood proteins occurs and the administration of blood plasma would appear to be indicated.

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PENICILLIN PROGRESS*

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The most important single advance which dominates any present discussion of the use of penicillin, is that the processes of manufacture have now been placed on so very large a scale in Great Britain and the United States of America that both the British and the American fighting forces have ample supplies and there is an increasing amount for civil use. This enormous increase of supplies should quite soon have a substantial influence on the outlook of those physicians and surgeons into whose hands penicillin comes.

The changing point of view may be illustrated historically. In the great majority of the earliest cases all other kinds of treatment, including surgery, had been used and had failed when, as a last resort, penicillin was tried. This initial mode of using penicillin was perhaps in some ways fortunate as it enabled a clear demonstration to be given of what its remarkable combination of properties—already well known to the laboratory workers—were capable of in the clinic, for example in the most desperate cases of staphylococcal infection. It also led, perhaps naturally, to the idea that penicillin was of use primarily to save lives and—for the time being, at any rate, owing to its extreme scarcity—only after all other possible methods had been tried. This usually meant that disease processes were far advanced before the institution of penicillin treatment. Now, with the relatively great abundance of penicillin available, the time has come when it is no longer necessary to try other forms of treatment in diseases regarding which accumulated knowledge has shown that penicillin will be the most effective therapy at present known. In other words, cases to be treated with penicillin should be treated early. From here it is but a step to contemplate the use of penicillin prophylactically to avoid infection rather than to treat it. This evolution has indeed been seen already in the treatment of war wounds. The first tentative explorations in 1942 were made on wounds which had remained septic for a very considerable time and had not responded to other forms of treatment. The next set of casualties, treated in 1943 were of 6 weeks' duration or longer, and were all chosen for treatment because of their septic condition. A little later, in the Sicilian campaign, it was possible to treat casualties between three and four days after wounding and to demonstrate on these men that even septic wounds could at this stage be sutured successfully when penicillin was employed in one way or another.

A further step was taken in the Western European theatre of war, where, much larger stocks of penicillin being by that time available, repeated or continuous intramuscular injection was ordered from the earliest possible moment for every man who was at all seriously wounded, with the idea that sepsis might be avoided, especially when definitive surgery came to be carried out.

The idea of using penicillin prophylactically has as yet made little headway in civil surgical and medical practice, except perhaps in the most serious cases of accident. The possibilities of its use in minor industrial accidents and so forth have scarcely been realized, although a clear indication of what can be accomplished by a careful combination of surgery and penicillin even when sepsis is established was shown as long ago as early in 1944 (M. E. Florey and Williams). In short, it would seem of the utmost importance at the present time that the idea that penicillin is to be used only as a last resort in serious cases should be superseded by the idea that it should be used to diminish minor as well as major incapacity, to reduce length of stay in hospital, and to ensure that functional damage due to accidents is not made worse by avoidable sepsis. No doubt this wider use may result in waste of penicillin by those not familiar with its properties or the results to be expected, but probably by now such losses can be borne with equanimity.

It is unnecessary to repeat here the essential points that all must know, but even

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now it is necessary to be on guard against falling into the error of using the drug in a routine rule-of-thumb way, without clearly understanding the aims involved, what it is possible to accomplish and how to attain the desired end.

Reports are appearing in which it is stated that penicillin has "failed" in diseases in which success might have been expected to ensue from its use. A good general rule to adopt is that it is incumbent on the physician or surgeon to find out the cause of the failure. When success is not obtained it is frequently the fault of the medical attendant, who may have failed to use the drug in the best way; and if any failure does occur it should clearly be understood that, provided the organism is sensitive, it is a failure of penicillin used in that particular way and not necessarily of penicillin in that disease.

THERAPEUTIC RANGE

Probably all the numerically important microbial diseases have now been investigated for susceptibility to treatment by penicillin. Nothing has emerged to shake the opinion that only those diseases caused by sensitive organisms can be successfully treated. The following is a list of the organisms which are sufficiently sensitive to penicillin to be within its therapeutic range.

Pathogenic micro-organisms sensitive to penicillin

* <i>Actinomyces bovis</i>	<i>Erysipelothrix rhusiopathiae</i>
* <i>Anaerobic streptococcus</i>	<i>Fusiformis dentium</i>
<i>Bacillus anthracis</i>	<i>Haemophilus ducreyi</i>
<i>Borrelia recurrentis</i>	<i>Leptospira icterohaemorrhagiae</i>
<i>Borrelia vincenti</i>	<i>Neisseria catarrhalis</i>
<i>Clostridium histolyticum</i>	<i>Neisseria gonorrhoeae</i>
<i>Clostridium oedematiens</i>	<i>Neisseria intracellularis</i>
<i>Clostridium perfringens</i>	<i>Spirillum minus</i>
<i>Clostridium septique</i>	* <i>Staphylococcus albus</i>
<i>Clostridium sordelli</i>	* <i>Staphylococcus aureus</i>
<i>Clostridium sporogenes</i>	<i>Streptococcus pyogenes</i>
<i>Clostridium tetani</i>	* <i>Streptococcus viridans</i>
<i>Corynebacterium diphtheriae</i>	<i>Treponema pallidum</i>
* <i>Diplococcus lanceolatus</i>	Viruses of psittacosis

* Strain variation in sensitivity

It is important to note that although the species listed are in general sensitive, there are within some of them individual strains which are relatively resistant. This is very striking, for instance, in the staphylococci, some of which are naturally resistant, and *Streptococcus viridans* also varies. Those species marked with an asterisk have been shown to have this strain variation. It is obvious that poor clinical results might be anticipated in the treatment of a disease caused by an insensitive strain of a usually sensitive species. In the early days, for the sake of economy, insistence was laid on ascertaining in every case before beginning treatment that the organism was sensitive. With much more penicillin available this is not now necessary, and valuable time may be lost by such an investigation, but the determination of the sensitivity of the organism is, however, of importance when the anticipated clinical result is not obtained.

The list of insensitive organisms is a long one—only the more important species are here listed. It should be emphasized that the tubercle bacillus is not within the therapeutic range.

Pathogenic micro-organisms relatively or very insensitive to penicillin

<i>Actinomyces necrophorus</i>	<i>Pasteurella tularensis</i>
<i>Bacillus mycoides</i>	<i>Proteus</i>
<i>Brucella abortus</i>	Protozoa
<i>Brucella melitensis</i>	<i>Pseudomonas aeruginosa</i>
<i>Escherichia coli</i>	<i>Salmonella aertrycke</i>
Fungi (pathogenic)	<i>Salmonella enteritidis</i> (Gärtner)
<i>Haemophilus influenzae</i>	<i>Salmonella paratyphi</i>
<i>Haemophilus pertussis</i>	<i>Salmonella schottmülleri</i>
Koch-Weeks bacillus	<i>Salmonella typhimurium</i>
<i>Listerella (Listeria) monocytogenes</i>	<i>Shizella dysenteriae</i>
<i>Monilia albicans</i>	<i>Streptobacillus moniliformis</i>
Morax-Axenfeld diplococcus	<i>Streptococcus faecalis</i>
<i>Mycobacterium tuberculosis</i>	<i>Vibrio comma</i>
<i>Pasteurella pestis</i>	Viruses except those of psittacosis

A suggestion has been made by Helmholz and Sung that infections of the urinary tract by resistant organisms such as *Proteus* and even by some strains of *Escherichia coli* may be amenable to treatment with penicillin because of the great concentration effected by the kidneys during excretion, but so far this lacks clinical proof.

A number of diseases have been treated which are of unknown aetiology but are possibly caused by some infectious agent, but none of these appear to be affected by penicillin. In this group can be included rheumatic fever, rheumatoid arthritis, fibrositis, Hodgkin's disease and the leukaemias.

Mode of action of penicillin

Fleming¹ in his original paper recorded the observation that his penicillin broth had a slow bactericidal action on small inocula of staphylococci in nutrient broth and under certain conditions had a lytic effect on suspensions of staphylococci. Nevertheless in 1932 he gave it as his view that "it is unlikely that it acts by killing the bacteria directly", and again in 1940 and 1941 he stated it to be bacteriostatic.

The work on the oxygen uptake of 24-hour cultures of staphylococci at Oxford (Abraham and his colleagues) showed that the uptake was unaffected by even high concentrations of penicillin, and that organisms could always be cultivated from such suspensions. The view was expressed that penicillin was a bacteriostatic agent. In 1942 Hobby, Meyer and Chaffee showed that when streptococci, pneumococci and staphylococci were actively growing, penicillin exerted a powerful bactericidal action although complete sterilization was not effected, and these workers confirmed that under conditions unfavourable for growth penicillin had no bactericidal action. Their views have been fully substantiated by themselves and others (Hobby and Dawson^{1,2}, Miller and Foster, Rammekamp and Keefer, Rantz and Kirby²), and in addition the conditions have been formulated under which the lysis occurs of staphylococci and certain other organisms (Smith and Hay, Fisher, Bigger^{1,2}, Garrod, Todd, Knox, Chain and Duthie, Gardner). There is no doubt that penicillin is bactericidal for organisms placed in conditions in which they can grow. Unfortunately, even under growing conditions there are usually some organisms which, for reasons at present unknown, are not killed, to these Bigger has given the name of "persisters".

The methods for the therapeutic application of penicillin were founded on the view that the drug was a bacteriostatic substance and that the ultimate removal of infecting organisms largely depended upon the body defences such as the leucocytes. Does then the clear demonstration of the bactericidal power of penicillin necessitate a modification of clinical practice? At present there is no evidence that such is called for—indeed, on the contrary, more and more voices are being raised to insist that if all organisms are to be eliminated from the body and the risk of relapse avoided, penicillin administration should be continued for a longer time than at first sight appears to be necessary. On the evidence of *in vitro* experiments, Bigger has proposed the intermittent administration of penicillin, on the assumption that the persisters will start dividing when penicillin is withheld and so become susceptible to its action. There is, however, no evidence that penicillin prevents these persisters from dividing in the first place, and there are as yet no clinical or animal experimental observations to support Bigger's suggestion. Until these can be offered there is no indication for giving up the methods which have been successfully used in thousands of cases.

METHODS OF ADMINISTRATION

Penicillin is an acid which readily forms a large number of salts. The first salt to be used in the clinic was the sodium salt but the partially purified material used clinically is, unfortunately, very hygroscopic, when it is exposed to the air it rapidly takes up moisture, after which it is apt to deteriorate. At the present time the bulk of penicillin is dispensed in the form of the sodium salt, in sealed ampoules. The calcium salt is easier to handle since it is not hygroscopic and, although it is somewhat more toxic than is the sodium salt, it can now be used with success for all clinical purposes. Both these salts are easily soluble, and can be dissolved in sterile water or saline to any required strength for injection.

The first crude preparations of penicillin were not always stable even when dried. The factors involved in this lack of stability have been gradually unravelled, one of the most important of them being insufficient drying. Another point is that stability seems to be related to the degree of purity, so that the present commercial prepara-

tions, which may contain 50 per cent or more of pure penicillin, are much more stable than was the early material, which contained perhaps 5 per cent or less. Although it is a wise thing to store penicillin in the cold this procedure is less urgent than it was, and there is no doubt that good samples of dried penicillin powder in sealed ampoules will keep for long periods at room temperature. The stability is still variable once the penicillin is in solution and for that reason solutions should be used as fresh as possible and should not be kept for more than a day or two. In addition there is the danger of the penicillin becoming infected with air bacteria. The accidental introduction of a few air bacteria which produce penicillinase may in the course of a day or so result in a very serious diminution of penicillin potency, or even in its complete abolition. Further, if an insensitive organism, such as *Pseudomonas aeruginosa*, contaminates a solution, serious results may be produced when the solution is injected.

Penicillin, as is well known, may be given either by way of the blood stream or directly by means of local application, so as to reach the areas harbouring infecting organisms. It is convenient to consider methods of administration under four headings, as follows.

Injection methods

It was shown by the original animal experiments that penicillin is readily absorbed after subcutaneous and intramuscular injection, and as the result of this work penicillin was administered to man by the parenteral in preference to the gastro-intestinal route, by which losses were known to occur. Penicillin, unfortunately, is rapidly excreted by the kidneys, so means have to be adopted to supply relatively large amounts of it in order to maintain a sufficient level in the body fluids. This may be accomplished by continuous intravenous administration, but with the disadvantage that thrombosis of the vein is liable to occur if administration has to be continued for more than a day or two. Judging from accounts in the literature this method is less used now than was formerly the case; it is possible that better results might be obtained by combining small amounts of heparin with the infusion fluid (Martin). Intermittent intramuscular injection is free from this disadvantage and is simpler to give, but it is annoying to the patient and is often painful, perhaps because of impurities in the penicillin. At the present time it is probably the most widespread method in use, and it gives good therapeutic results. Active search is going on, however, for methods which will improve on or supersede this simple form of administration.

Continuous intramuscular injection.—This method was first described by Morgan, Christie and Roxburgh, who utilized an ordinary blood transfusion apparatus and infused two pints in twenty-four hours into the muscles of the thigh. Although satisfactory blood levels were obtained, in two cases abscesses developed due to the presence of *E. coli* at the site of the needle. Various forms of apparatus have been devised to enable much smaller amounts (100–200 cubic centimetres in twenty-four hours) of fluid to be administered. These devices work on a drip principle (McAdam, Duguid and Challinor) or depend upon force generated by a motor for the steady pushing in of the plunger of a syringe (Last). These methods are almost painless and cause little disturbance to the patient, but they need attention, especially in the early stages, in order to ensure a regular flow and to avoid infection round the needle. One good rule is to allow only a skilled operator working in sterile conditions to make the initial adjustments. Many successful continuous injections have been given by army surgeons using the ordinary blood transfusion apparatus, giving about 500 cubic centimetres a day. Methods of infusing the fluid into the bone marrow, for example of the sternum, have been described (Kolmer) but up to the present have received little attention.

An interesting point emerged during the trials of continuous intramuscular infusions. It was found that certain samples of rubber tubing inactivated penicillin (Cowan). It is therefore essential to check this point with each apparatus and to use only tubing proved to be harmless.

Slow absorption.—Another approach has been to try to prolong the effect of a single injection by slowing the rate of absorption. Various methods have been suggested. Meyer and his collaborators (Meyer, Hobby and Chaffee; Meyer, Hobby and Dawson) thought that the relatively inactive methyl and ethyl esters of penicillin, which are almost insoluble, might be slowly hydrolysed in an injected deposit to the active material. Unfortunately the hydrolysis appears to be too slow a process to serve the

desired purpose Mechanical means have been proposed and of these the method introduced by Romansky and Rittman^{1, 2}, in which calcium penicillin is suspended in peanut oil with a small percentage of beeswax, appears to be the most promising. Absorption is certainly prolonged, these observers state that a single injection of 300,000 units of penicillin in their base maintains a reasonable blood level for twenty-four hours. This dose is about three times the total dose necessary to achieve the same effect by continuous or intermittent injection in a watery medium. Other methods to effect slow absorption have been tried, for example injection with a vasoconstrictor such as adrenaline (Fisk, Foord and Alles, Parkins and his co-workers) or cooling of the part after injection (Trumper and Hutter).

Oral administration

Clearly this is the method to be preferred if it can be made practicable. Penicillin is absorbed from the small intestine, but the difficulty is to avoid the considerable destruction which occurs during passage through a normal acid-secreting stomach. Various methods, such as administration with alkali by means of a duodenal tube or in coated capsules, were tried in the earliest days (Abraham and his colleagues, Florey and Florey) but when it became clear that these were relatively wasteful the trials were abandoned for the time being. With the greater supplies now available attempts are being made to assess the possibilities of oral administration. In general the idea is to combine the penicillin solutions with some sort of buffer (for example sodium citrate, egg albumin, milk), to enclose the material in a capsule or to mix it with oil or fat. (The few preliminary trials published at the time of writing are summarized by Heatley.)

It is certain that an effective blood level can be obtained by some of these methods but, as compared with intramuscular injection, all those proposed up to the time of writing are "wasteful" since they use three or four times as much penicillin in the extravagant way for the comfort of the patient is not clear, for instance it may perhaps be justifiable in the treatment of gonorrhoea when the giving of intramuscular injections for a sufficient length of time may be difficult to arrange in civil practice. But it may be noted that Romansky and Rittman's injection method also demands a dose of this size.

Postscript on oral administration—With the present rapid increase in the cheapness and availability of penicillin, many workers are attempting oral administration and are publishing the results of the first clinical trials. At the time of writing (30th October 1945) the following have recently appeared. Burke, Ross and Strauss enclosed sodium penicillin in a double gelatin capsule which was then hardened in formol (formaldehyde) and alcohol. Absorption, as demonstrated by inhibition in the blood, was better when the dose was given before than when it was given after a meal. Ross and others reported that 100,000 units in these capsules three hourly cured children with gonorrhoea, pneumonia and cellulitis. Finland and his collaborators and Bunn and his collaborators gave 50,000–100,000 units two hourly in water without special protection, and although they had shown that when penicillin was given in this way after meals absorption was very irregular, they obtained good results in patients with pneumococcal and gonococcal infections. Finland and his associates pointed out, however, that infections by less sensitive organisms such as many strains of meningococci and *Staphylococcus aureus* and some strains of *Streptococcus viridans* could not be expected to respond to this treatment.

A more prolonged effective level in the blood has been obtained by mixing the penicillin before administration with aluminium hydroxide, on which some of it is adsorbed. Welch, Price and Chandler showed that when 100,000 units were given in this way, penicillin could be detected in the blood twenty four hours later in five out of eleven subjects. Apparently the adsorbed penicillin was released slowly during the whole period. When four doses of 25,000 units were given at intervals of two hours the level maintained in the blood was higher and penicillin could be detected there for twenty-eight hours. Equally promising results were reported from the use of basic aluminium aminoacetate by Krantz, Evans and McAlpine, but they terminated their experiments at seven hours. If these experiments are confirmed they will introduce a method of oral treatment comparable in economy with continuous intramuscular or intravenous administration.

Other methods

The suggestion has been made that adequate penicillin absorption can occur through the lungs (Bryson, Sansome and Laskin) during the inhalation of atomized penicillin solution. Knott and Clark, and Mutch and Rewell, went further and suggested that economical penicillin administration could be provided by dispersing penicillin as an aerosol in the atmosphere of a room. They showed that inhibitory levels could be maintained in the serum and suggested that the method might be particularly useful in the treatment of children.

Another approach to the problem of simplifying the administration of penicillin depends upon the conception that penicillin is actively secreted by the tubule cells of the kidney. That this is very likely has been shown by the work of Rammelkamp and Bradley, of Beyer and his co-workers and of Rantz and Kirby¹. Rammelkamp and Bradley thought that penicillin might be kept in the body longer if it had to compete for excretion with diodone (Diodrast), a substance which is also excreted in the tubules. This they found to be the case. Beyer and his collaborators suggested the similar use of *p*-aminohippuric acid, which also passes through the tubule cells and is remarkably lacking in toxicity. Their experimental results on dogs and on man supported their ideas, but at the time of writing there are no reports on the use of this method in the treatment of disease.

The reader will realize that much thought is being expended on this apparently simple matter of administration.

Dose

As the result of experience gained *in vitro* and on animals, it was from the outset of clinical work considered necessary to aim at having always present in the blood sufficient penicillin to inhibit completely the organism it was desired to eliminate. It was apparent that to detect small although sufficient amounts in the blood a more delicate test was necessary than the cylinder and plate method used for assay. Several procedures have now been proposed, all depending upon inhibition of growth of a staphylococcus or a streptococcus (Rammelkamp; Fleming²; Kirby and Rantz). In the method adapted by Heatley (Garrod and Heatley) from Wright's slide cell technique the test staphylococcus is grown directly in the patient's serum. It was thus found (Florey and Florey) that after an intramuscular injection of 15,000 units an inhibitory concentration of penicillin could be detected in the blood of an adult for from two and a half to three hours. On this basis it was suggested that, for an adult, 15,000 units every three hours by the intramuscular or intravenous route should be adequate for the treatment of most infections, since such a dose provided a penicillin level in the blood which was well above the inhibitory level for most of the time and below only for a short time, if at all. Independent workers in America—Rammelkamp and Keefer, for instance—arrived at the same conclusion and as a consequence a basic or standard dose of 15,000–20,000 units every three hours (or 100,000–120,000 units a day by continuous administration) has been widely adopted.

Now that penicillin is more abundant a tendency is noticeable, especially in America, to raise this dose considerably in many cases. It should be clearly understood that doubling the dose does not double the length of time that penicillin is retained in the body. A greater concentration is reached in the blood for a short time after injection, but the efficiency of the kidneys in excreting penicillin is such that the duration of an effective blood level is not much lengthened.

In spite of this, increasing knowledge of the variation in sensitivity within the various sensitive species suggests that in certain cases the dose should be increased in the attempt to inhibit a relatively resistant strain. Penicillin is still the one drug which does not give rise to anxiety because of the possibility of its producing toxic effects, and from the patient's point of view it is certainly better to give too much rather than too little, since harm may be done by under-dosing but not by over-dosing. There is a risk, too, if insufficient penicillin is given, of developing penicillin-fast strains of originally susceptible organisms. Fortunately the risk of this does not appear to be great in infections in man, but it has occasionally been shown to occur (Florey and Florey; Putney; Selbie, Simon and McIntosh).

Local administration

The methods employed for local administration have changed little from those first

introduced Administration of the calcium salt as a powder diluted with a sulphonamide is still widely practised, especially in war surgery. It is used in strengths varying from 2 500 to 5,000 units per gramme of sulphonamide. Administration in solution (250–500 or sometimes 1,000 units per cubic centimetre), either through tubes sewn into a wound or in the form of drops or a spray, is also commonly carried out. Ointments are useful, for example in the treatment of burns, but objection has been taken to Lanette wax—the material commonly employed in Great Britain as a base (Clark and his collaborators)—on the ground that penicillin does not diffuse out of the cream. Nevertheless successful clinical results are obtained when the wax is used. It is probable that we still have to find the ideal base for the incorporation of penicillin. In ophthalmology a soft paraffin ointment has been used.

A preparation for infections of the mouth such as Vincent's angina has been suggested by MacGregor and Long—a gelatin pastille, incorporating penicillin, which is dissolved slowly in the buccal sulcus. This is useful not only for the treatment of established infection but for prophylaxis after tooth extraction or operations on the jaw. It is suggested that lamellae of lactose and penicillin are useful in ophthalmology (Neely and Cross) in addition to the usual solutions and creams. The more extravagant statements about the advantages of the incorporation of penicillin in lipstick need not be taken too seriously.

Since surgeons will no doubt continue to argue the relative merits of giving penicillin locally or systemically for wounds and localized lesions, it may be helpful to put down here some of the points to be considered. The *sine qua non* of local application—full access to all traumatized or infected tissue, obtained if necessary by surgical means—is assumed.

Local application has the following advantages

- (1) Its employment is painless and free from discomfort
- (2) An inhibitory concentration can be maintained for from twelve to seventy two hours by a suitable application so that the maximum frequency of treatment is twice a day
- (3) Much higher concentrations can be maintained than by systemic administration thus bringing relatively resistant organisms within the therapeutic range
- (4) It is essential for full effect in places such as the cerebrospinal space, and in the pleural and joint spaces
- (5) In an area where surgical drainage needs to be established the same tube can be used for drainage and instillation
- (6) Instillation through tubes and the application of powders and creams can be carried out by the nursing staff
- (7) In certain conditions the patient can be treated as an out patient
- (8) The amount of penicillin needed for effective local treatment is a small fraction of that required for systemic treatment
- (9) It has recently been shown (Florey and Heatley) that the instillation of a single large dose such as 120 000 units into a cavity (for instance an empyema) will not only accomplish local treatment, but will also produce an inhibitory level in the blood serum for as long as forty-eight hours. The same consideration probably applies to wounds.

Against local treatment is urged the danger of introducing Gram negative organisms such as *Ps. aeruginosa* (Botterell and Magner), but this would seem to be mainly a question of technique.

DURATION OF TREATMENT

Whereas the daily dose of penicillin which is effective by the parenteral route can be stated with fair exactness, it is often a matter of considerable difficulty to decide on the duration of treatment either local or systemic. It has always appeared to me and to my colleagues that penicillin should be continued for some days after all clinical signs of infection have disappeared or the lesion has healed, or, when bacteriological examination can profitably be made, until after the causative organism has disappeared. This view is receiving increasing support and recent American contributions again emphasize the point. In looking through the literature one is struck by the fact of inadequate length, as well as in some cases an inadequate total daily dose. Experience abundantly shows that relapses may occur unless treatment is continued for longer than, from a superficial point of view, might be considered necessary. It would appear unwise to consider giving penicillin in interrupted courses. Physicians and surgeons are accustomed to give sulphonamides in this way because of the fear of toxic symptoms—they prefer to stop early and to start again if necessary. It is generally agreed that penicillin is remarkably free from toxicity even when it is

injected in very large amounts. Occasionally a patient is sensitive, and a dermatitis or urticaria develops. Rarely there are joint swellings. Such sensitivity is in some cases due to the penicillin itself, but in others may be caused by impurities. Usually the symptoms subside even although the administration is continued, but occasionally the administration has to be stopped.

In contrast to the position in regard to the sulphonamides there is with penicillin no reason to fear kidney complications, which have never been described. Neither is there evidence that the haemopoietic system is affected adversely; indeed there is often an increase in haemoglobin and erythrocytes during administration, as the infection is overcome.

PENICILLIN IN INJURIES AND DISEASES

War wounds

It is particularly in war wounds that penicillin has demonstrated during the last two years how much can be done to control sepsis. It was first shown in 1943 at hospitals in Tripoli and Sousse that the local application of penicillin would enable a large proportion of soft tissue wounds to be sutured successfully, even although many were frankly purulent (Jeffrey and his colleagues). The technique, which consisted in the application of penicillin and sulphanilamide or sulphathiazole powder, either alone or in conjunction with penicillin solution instilled through tubes, has now been tried on a considerable scale in Italy (among the relevant papers are those of Brown; Capper; Hendry, Gledhill and Price; Turner, Murray and Fowler; Atkins and Holden; McEwen, Bickerton and Pilcher; Bhatia). The results are very favourable and it is quite clear that with penicillin it is possible to close the majority of wounds without risk. The resulting benefit is reflected not only in quicker healing but also in the much better final functional results. From the North-west European theatre the same story is being told, although as yet few published accounts have appeared. Such papers as that of Burns, Young and Muller indicate the amount of functional restoration which can be obtained after joint injuries.

Nearly all reports emphasize the important part that proper wound excision plays in obtaining the best results after suture. No doubt this is true but it is only fair to remark that there is at least one important reason why wound toilet is now, in general, thorough. The young surgeons who perform it are rightly acclaimed as doing their job efficiently, and they are encouraged by the knowledge that they can make extensive incisions for exploratory purposes or for excision because these will soon be sutured at a base hospital. In other words, the very possibility of suturing the great majority of wounds has acted as a stimulus to those working in the forward areas to perform not less careful but more careful surgery.

It is of no profit to try to allot marks for the part played by surgery in comparison with chemotherapy in obtaining good results in wounds, although such discussions will no doubt be renewed from time to time. What has been quite clear ever since the first experimental results were obtained with penicillin on animals is that the surgeon has at his command a drug which, when properly used, can control all serious cases of sepsis caused by staphylococci and streptococci. The use he makes of the drug depends upon his skill and ingenuity. The excellence of the results now being reported shows how well the younger men in particular have grasped their opportunities.

In the early work at Tripoli promising results were obtained from the use of penicillin administered parenterally in treating fractures (Jeffrey); since then fractures and the more serious wounds have been treated both locally and systemically and by a combination of the two methods (e.g. Burns and Young). Corresponding improvement of results has been obtained in chest and head surgery (D'Abreu and Litchfield; Cairns¹).

Although in the British Army in Italy emphasis was placed chiefly upon the local use of penicillin, American surgeons in that theatre used almost exclusively the parenteral route for treating war wounds. They too emphasize the need for meticulous surgery, and their results have been equally encouraging, as a paper by Churchill, their Consulting Surgeon, shows. Similar evidence comes from North-west Europe, although few reports are to hand at the time of writing.

No doubt penicillin has saved some lives which would otherwise have been lost, but it may be emphasized again that among its chief benefits have been the shorter healing time and the improved functional result, the lessened length of stay in hospital

and the fact that in far fewer wounded men does there develop a condition of chronic sepsis, with its serious consequences

Gas gangrene

It is not possible, unfortunately, to give any clear-cut answer regarding how much penicillin has achieved in the prevention or treatment of gas gangrene. It is certain that the majority of the gas gangrene organisms are sensitive to penicillin and that the substance can be shown to be effective in experimental lesions caused by such organisms (Chain and his colleagues, Hae). For various reasons it has proved to be more than usually difficult to make decisive observations on the condition in warfare, but from the scanty reports it seems to be likely that the methods tried for treating developed gas gangrene have not been entirely adequate.

As regards prophylaxis, it seems to be probable that one of the reasons for the low incidence of gas gangrene in the North-west European campaign was the general use of penicillin in large doses, from the earliest time after wounding, for those most severely injured. In none of the patients in 4,000 consecutive cases reaching a transit hospital in the first six weeks after D Day, who had received penicillin prophylactically, had gas gangrene developed, although these were the patients most liable to be so affected (Fisher and his collaborators).

Osteomyelitis

It is becoming clear that in many cases of acute haematogenous osteomyelitis, if the patients are treated by parenteral administration of penicillin before thrombosis of the nutrient arteries has occurred, they may recover without surgical intervention. Others recover after simple opening or aspiration of a localized abscess. It cannot be stressed too strongly that early administration is of the utmost importance in these cases if the maximum benefit is to be obtained from the drug.

Reports on the treatment of chronic osteomyelitis are not so encouraging. It is clear, however, that, provided penicillin is employed before and after operation, surgeons may operate freely on infected bones without causing a flare-up of the disease or dissemination of bacteria. Thus is opened up the prospect of safe radical surgery to remove dead bone even when active infection is present. With the wider application of this knowledge it is likely that results in chronic osteomyelitis will improve.

Syphilis

Nearly all the knowledge concerning the treatment of this condition derives from sources in the United States, where a large and diversified coordinated programme is being carried out (as is shown by many papers, for example those of Mahoney and his colleagues and of Moore and his co-workers). Both experiments on animals and observations on man show that, so far as can be determined by microscopical examination of exudates, penicillin can cause a rapid disappearance of spirochaetes from any lesion.

The schemes of treatment tried up to the present have apparently been influenced, so far as the armed forces are concerned, by the necessity of returning men to duty quickly, and attempts have usually been made to effect a "cure" in as short a time as seven and a half days, using up to 2.5 million units of penicillin. Apparent cure has been effected in a considerable number of cases on these schedules, but there have also been many relapses. In this connexion the experiments on rabbits performed by Ercoli and Lafferty are of interest. They showed that, given over a short period, even enormous doses (up to 282,000 units per kilogram of body weight) failed to produce complete disappearance of the spirochaete from the body in rabbits. It appears that the power of penicillin to deal with the spirochaete of syphilis may be called in question if, as seems to be likely, cases of relapse become at all common. Before it can be said that the drug has failed it is necessary to enquire carefully into the method of its administration. As in so many other diseases of a chronic nature, it is probable that treatment continued over some weeks, or if necessary months, using relatively small doses, will yield better results than will large doses given for a short time. The exploration of the treatment of syphilis, at all stages—including congenital syphilis—continues, and no final opinion on the results even of present methods of treatment can be given for some years. If they should not be satisfactory there will still be ample scope for trying other, and especially longer, courses.

Gonorrhoea

Acute gonococcal infection in both the male and the female reacts with astonishing rapidity, as many papers (for example those of Sternberg and Turner and of Riba, Schmidlapp and Bosworth) bear witness. Again, considerations of the conservation of manpower have played a part in formulating the treatment of the disease. From the point of view of the Services it is highly desirable to cure gonorrhoea in the shortest possible time, if possible without admission of the patient to hospital. This aim has resulted in an endeavour to cure gonorrhoea between dawn and dusk. The astonishing fact is that a course of eight or of ten hours does free a very large proportion of patients from gonococci, as shown by the ordinary tests, although with experience on larger numbers it is possible that some may be found to be carriers. It would be a pity if penicillin were to be discredited in connexion with gonorrhoeal treatment because of relapses and carrier cases. Here again it seems that the margin between the elimination of signs of infection and the ending of treatment has been cut much too fine under the pressure of conditions in the armed forces. In civil practice it might well be profitable to prolong treatment for two or three days in order to give the body the best chance to deal with the cocci completely.

Endocarditis

Subacute bacterial endocarditis has attracted considerable attention, since many of the strains of *Str. viridans* responsible for this intractable disease are sensitive to penicillin. The early reports (Florey and Florey; Herrell, Nichols and Heilman) were discouraging, but with further experience the results are much more hopeful. In the first promising series (Loewe and his co-workers) heparin was used with the penicillin, but this does not appear to be necessary since equally good results are now reported with penicillin alone (Dawson and Hunter; White, Mathews and Evans). It is obvious that in a disease such as this it will be impossible for some years to give a final judgment. Treatment has usually been continued for a number of weeks but the size of individual doses of penicillin has varied. Probably in this disease again it will eventually be shown that it is the *length* of treatment which is important rather than a heroic daily dosage. Support for this opinion has recently been obtained experimentally (MacNeal and his colleagues). The infecting *Str. viridans* is, unfortunately, sometimes relatively insensitive to penicillin, so that in endocarditis it is important to make a bacteriological investigation of sensitivity at the start of treatment.

PENICILLIN AND THE SULPHONAMIDES

Synergistic action

Some workers (Ungar; Bigger²; Soo-Hoo and Schnitzer; Chain and Duthie) have shown that *in vitro* and in the experimental animal sulphonamides have a synergistic effect when combined with penicillin. Chain and Duthie have demonstrated that there is a marked effect when sulphadimethylpyrimidine (sulphamezathine) is used.

The sulphonamides have been widely administered concurrently with penicillin, but few observations have been made on man which are much help in assessing whether in practice this is valuable or not. It is now stated that pneumococcal meningitis is most effectively treated when sulphadiazine administered by the mouth is combined with penicillin given intrathecally or intraventricularly (Cairns²). In combining the two drugs it should be kept in mind that the sulphonamides produce unwanted side-effects and that the patient frequently feels ill after taking the drug. It is not yet clear whether any sufficiently great counterbalancing advantage is obtained in the form of a better or a more rapid clinical response.

CONCLUSION

It might be assumed that because little is said or written about chemical investigations on penicillin none are being done. This would be wide of the mark. There is in fact a great accumulation of knowledge, but it must remain secret for the time being. Advances in chemical knowledge may in the next few years bring great changes in methods of administration and in the range of organisms affected. Much of our present painstaking effort to determine optimum dosage for certain conditions may then become obsolete.

We are at the present time witnessing the production of data by hundreds—if not thousands—of observers and their efforts for the most part result in the detailed filling in of the outline already established. At the same time, with wider dissemination of knowledge of the drug, and increased experience in its use, the standard of the results achieved is steadily rising. To fill in the details of the various aspects of the therapeutic work is in itself a great labour, but clinicians should ever be mindful of the immense amount of work, both of a chemical and biological nature, which was expended in the first assessment of the power of the drug and which, even now, goes into the production of the yellow powder before it reaches their hands. The rapidity of progress and the scale of the effort can be gauged by the fact that it is scarcely five years since penicillin had to be recovered from the urine of patients for re-injection, and since even the drops on the side of a test tube were saved.

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RADIOLOGY

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The past year has shown no outstanding developments in the field of radiology. Some progress has been made, however, in certain fields, each of which is surveyed in the pages which follow

ALIMENTARY SYSTEM

The small intestine enema

The most important contribution to the radiology of the alimentary tract has been the introduction by Schatzki of the small intestine enema. Although physiologically the small intestine is more important than either the stomach or the colon, it has received less attention radiologically than has either of these two, mainly on account of the technical difficulties of its examination. The investigation of the small bowel during the routine opaque meal examination is a laborious and time consuming procedure. The filling of the small intestine is difficult to control, and an adequate demonstration of its entire course is often a matter of chance, since this is dependent upon the manner in which the stomach empties its contents. The small intestine enema offers greater possibilities than any other method for the detection of organic disease in this portion of the tract.

The small intestine is filled through a soft rubber tube with a metal olive tip which is passed into the duodenum by way of the mouth, 500–1,000 cubic centimetres of a barium sulphate suspension being run in from a small container held above the patient's head. A continuous flow of the suspension is essential, because any interruption of the flow will delay the examination. It is also important that the small intestine should be filled in the shortest possible time, the filling being controlled by screen examination. In the average normal case, the opaque solution reaches the caecum in 15 minutes, although occasionally, if there is a marked reflux of the barium into the stomach, the filling may be delayed. In pathological cases, the filling of the intestine takes longer, the average time being 37 minutes.

The primary purpose of the method is the detection of organic disease, it is of little value for the demonstration of functional changes in the small intestine. As a routine, the small intestine enema examination should be preceded by an investigation of the stomach and the duodenum. Its use is contra indicated in cases in which a marked mechanical or paralytic ileus is present, and it is inadvisable to employ the method when there is an active duodenal ulcer.

Among the advantages of the small intestine enema, not least is the saving of time occupied by the examination. Circumscribed lesions of the small intestine can be demonstrated with greater certainty. In cicatrizing enteritis, the extent of the lesion can be more accurately shown, and the extent of grossly normal bowel proximal to the lesion can be more precisely estimated, a point of considerable importance when the operability of a case is being considered. In this lesion, the opaque substance is sometimes spurted so rapidly through the narrowed area that it cannot be demonstrated unless the filling is actually seen during the enema examination. The method is extremely valuable for demonstrating the site of a small intestine fistula, and for visualizing the presence or absence of coils of small intestine within a hernial sac. In cases in which an adequate examination of the caecum, ascending colon and ileocaecal valve cannot be made by a rectal enema, on account of anal incompetency or because of spasm in the caecum or ascending colon, the small intestine enema is invaluable in showing these areas with a fluid barium sulphate suspension.

Avitaminosis

Attention has been drawn by Learner, Stauffer and Brown to the disordered function of the small intestine, and to the changes seen in its mucosal relief pattern in cases of avitaminosis. In early cases, the radiographic deficiency pattern is characterized by hypermotility and hypertonicity, and in advanced cases by hypomotility and dilatation. The small bowel shows abnormal segmentation. The mucosal relief pattern is coarsened and may be obliterated and the opaque medium tends to flocculate on the mucosal surface. In mild cases the changes are slight, and they are indistinguishable from normal variations. The x-ray signs are by no means characteristic of avitaminosis and are of limited value. Further work is necessary before the small intestine deficiency pattern can be accepted as reliable evidence of vitamin B complex deficiency. Similar changes may be produced by other causes, such as emotional disturbances. Nevertheless, as Learner and his co-workers point out, patients with functional gastro-intestinal disturbances as shown by radiographic changes in the small bowel mucosal relief pattern, deserve a trial of vitamin B complex therapy. These workers recommend the giving of yeast by mouth and of crude liver extract parenterally, and the addition of other components of the complex may be of value. In those cases which they investigated and which showed a moderate deficiency small intestine pattern, symptomatic improvement after vitamin B therapy was accompanied by improvement in the small intestine deficiency pattern.

Cholecystography

There is no general agreement concerning the significance of delayed contractility of the gallbladder during the cholecystographic examination after a fat meal, and the problem has been studied by Bacon. In twelve cases in which the gallbladder showed adequate concentrating ability and in which poor contractility after a fat meal was the only abnormal finding, operation revealed in eleven cases either inflammatory disease of the gallbladder or adhesions around the gallbladder or its ducts. After removal of the gallbladder, eight patients were relieved of pain in the right upper abdominal quadrant, two were clearly improved, and one died as the result of a pancreatic cyst with infection. The remaining patient showed no evidence of disease of the biliary tract, but a pre-obstructive carcinoma of the distal colon was found at operation. In this case, it was assumed that the poor emptying of the gallbladder was reflex in origin.

A normal gallbladder completely expels the dye in use in 1-3 hours after a fat meal. A gallbladder which has not emptied 50 per cent or more of its contents within three hours, indicates that there is abnormal biliary tract function, even when the delayed emptying is the only abnormal finding. The gallbladder expels the dye after a fat meal by tonic contractions initiated by cholecystokinin derived, in response to fat digestion, from the duodenum. Simultaneously, relaxation of the sphincter of Oddi and the duodenal musculature permit the entry of bile into the duodenum. Delayed emptying of the gallbladder may be due to absence of cholecystokinin formation. In the presence of organic disease of the gallbladder wall, the dye may nevertheless be sufficiently concentrated to have the appearances on the film of a cholecystogram but, because of the rigid character of its wall, the gallbladder may be unable to expel the dye, and it therefore remains radiologically visible for an abnormally long period. Functional derangements, such as spasm of the sphincter of Oddi, with a normally contracting viscus, may cause delayed emptying in the absence of organic disease. In those cases in which delayed emptying is the only abnormal finding at the cholecystographic examination, a course of medical therapy should be instituted. If at the end of this course re-examination shows that delayed emptying of the gallbladder after a fat meal persists or has not materially improved, it will usually be found that organic disease of the biliary tract is present.

RESPIRATORY SYSTEM

Primary atypical pneumonia

This condition is characteristically associated with epidemic tendencies rather than with sporadic cases. Epidemics occur most commonly in the late summer and in the autumn, when common diseases of the respiratory tract are at a minimum. It is believed that unaffected carriers may play an important part in the spread of the

disease Judging from published reports, it is a disease showing a rising incidence, and is a lesion of some importance on account of the long convalescence which is usual Many recent publications have added to our knowledge of its course and pathology The condition is an interstitial pneumonia and the pathological picture is that of inflammation of the bronchi and bronchioles with infiltration and exudation in the peribronchial tissues Localized areas of lung collapse are produced as the result of the blocking of bronchi and bronchioles by inflammatory exudate Most authorities agree that it is a virus disease, and this is borne out especially by the work of Eaton, Meiklejohn, and van Herick, in the majority of their cases the presence of an unidentified virus was proved Having transmitted to chick embryos a filtrable virus obtained from filtered sputum or a suspension of lung tissue, they were able to produce pulmonary lesions, similar to those produced by direct infection with human material, by the intranasal inoculation of the chick tissue into cotton rats In a small number of especially severe cases, Meiklejohn, Beck, and Eaton were able to confirm the presence of psittacosis like viruses

A brief recapitulation of the main points with regard to atypical pneumonia which has been discussed in previous volumes of Medical Progress, may be helpful The clinical picture is fairly well defined The incubation period is 1-3 weeks The condition most commonly attacks young adults The onset is gradual, with moderate pyrexia, aching, weakness, and loss of appetite The most troublesome symptom is an irritable and persistent non productive cough which tends to be relieved in a few days as the fever diminishes by lysis The pulse and respiratory rate are not much increased, and there is no appreciable leucocytosis (Owen) In uncomplicated cases, clinical recovery takes place in 1-2 weeks, but x ray signs may still be present after the patient has been clinically cured It is generally agreed that the patient should not resume his normal activities until the chest is radiologically normal Complications and recurrences are uncommon, and complete recovery is the rule

The use of x rays is the most important aid in the diagnosis, and the radiographic picture reproduces closely the known pathological changes Symptoms are usually in advance of the x ray signs, the earliest x ray changes being visible on the second or third day after the onset of symptoms The earliest x ray signs consist of accentuation of the hilar marking on one or both sides, with hazy densities or cloudy mottling projecting into the lung fields from the hilar region In the early stages, these changes seldom extend beyond the middle of the lung field As the disease progresses, there is a generalized increase in the pulmonary markings with patchy, dense, confluent opacities but the opacities are seldom well defined or homogeneous When the disease begins to abate, the entire pneumonic area starts to clear at once, but the accentuation of the bronchovascular markings is the last to subside The process seems to have a predilection for the lower lung fields, and may involve small portions of a lobe or one or more lobes completely As a rule, its radiological diagnosis offers little difficulty Occasionally, when the process is confined to the upper lobe, the radiographic appearances may simulate a tuberculous infiltration In the most severely ill patients a diffuse generalized mottling, resembling miliary tuberculosis, may be present (Needles and Gilbert) Following the progress of the condition by serial radiographs will usually leave no doubt as to the diagnosis, since the radiographic signs in atypical pneumonia usually clear completely in 2-3 weeks

Occupational lung disease in boiler scalers

In the study of industrial diseases of the lungs, Dunner has drawn attention to changes which are found in boiler scalers, and which have not been generally recognized The symptoms are not characteristic of any special lung disease and resemble those of chronic bronchitis and emphysema There is no definite correlation between the symptoms and the length of time the patient has spent in the occupation Dunner considers that any chest symptoms, however slight, in boiler scalers should suggest the possibility of occupational disease, and recommends x-ray investigation

The diagnosis of the condition is dependent upon the x ray findings Three types of x ray picture are differentiated In the first group, the lung fields show a uniform mottling, either fine or coarse, resembling that seen in miliary tuberculosis In the second group, some cases show, in addition, areas of infiltration, due to confluence of the smaller foci The localization, shape and extent of these areas of infiltration are not constant In the third group, the predominant finding is fibrosis

VASCULAR SYSTEM

Arteriography

The introduction of diodone as a contrast medium in arteriography appears to have made this a safe procedure; hitherto, arteriography has not been much employed in Great Britain. Apart from the dangerous possibility that arteriography might precipitate or aggravate gangrene, it was difficult to find a non-toxic and non-irritating contrast substance. Various media were tried. Among the earliest was sodium iodide 25 per cent, but this was associated with the risk of iodism and moreover tended to damage the endothelium of the blood vessels. The organic iodine compounds, such as Uroselectan B (iodoxyl), were tried. Although they eliminated the risk of iodism, they were irritating, and their accidental extravasation into the tissues during injection produced local necrosis. Thorium dioxide (Thorotrast) was used as a contrast medium, but it was soon found that it was taken up and retained in the reticulo-endothelial system. This substance, being radioactive, was liable to cause malignant or other changes. Diodone satisfies the requirements of a safe contrast medium. It is non-toxic and non-irritating, and the accidental extravasation into the tissues during injection produces no untoward effects.

Using diodone 50 per cent as the contrast medium, Learmonth¹ has described his technique for arteriography. To remove vasoconstrictor control, he recommends induction of spinal anaesthesia, 120 milligrams of procaine hydrochloride being given half an hour before injection. The vessel is exposed, being disturbed as little as possible, since this helps to avoid the local spasm which appears occasionally, even under spinal analgesia. Ten cubic centimetres of diodone 50 per cent, warmed to body temperature, is injected by a syringe, the needle being passed into the artery bevel downwards and parallel to its wall in order to prevent leakage of blood during its passage and to provide a long valvular tunnel which will be rapidly closed by interarterial pressure when the needle is withdrawn. Immediately blood appears in or is aspirated into the syringe, the medium is rapidly injected, and the x-ray exposure is made when the injection is almost completed. The needle is then withdrawn and a moist swab is pressed on the vessel at the site of puncture until oozing from the puncture has stopped.

Arteriography is not recommended as a routine procedure, but it may be usefully employed when clinical examination fails to give all the information required. It has been found to be of special value in the diagnosis and localization of thrombotic blockage of the main trunks in obliterative vascular disease, and in showing the extent of the collateral circulation. Learmonth² has encountered cases in which, after supposed ligation of a main vessel, an arteriograph has shown that only a collateral branch has been ligated. According to Ross, an arteriograph has a prognostic value by demonstrating the site of the main arterial stream blockage in arteriosclerotics. If the site is in the popliteal artery at the level of the femoral condyles, the prognosis is poor. If, however, the arteriograph shows a block high in the popliteal artery or in the femoral artery, there is a good chance of development of an adequate collateral circulation. Arteriography is being more largely employed as a preliminary to operation on traumatic aneurysms. It helps by outlining the sac of the aneurysm, showing its site and extent; furthermore, by compression of the main artery proximal to the sac before injection, the collateral circulation may also be demonstrated. Among other applications of the method is the location of the site of the fistula in arterio-venous aneurysm. It is necessary to compress the efferent vein of such a fistula during the interarterial injection.

OBSTETRICS

Intra-uterine fetal death

In the field of obstetrics, Roberts has recorded the presence of gas in the radiograph of the fetal circulatory system as a sign of intra-uterine death. The patient was examined 66 hours after the absence of fetal movements was first noticed. In a radiograph taken with the patient horizontal in the right lateral projection, gas was noted within the fetal shadow. The gas was seen as a spiral of fairly constant diameter, passing from the region of the fetal abdominal shadow to the peripheral zone of the uterine shadow. Two parallel narrow lines were seen in the lower portion of the fetal abdomen, extending from the umbilicus to the pelvis. Over the fetal liver area, a tree-like radio-

translucent area was present and there was a bilocular area over the fetal thoracic shadow, suggesting in size, shape and position the cardiac chambers. Finally a large oval area was situated over the shadows of the upper four fetal lumbar vertebral bodies. Although no other radiographic evidence of intra-uterine fetal death, such as overlapping of the cranial bones, was present, these areas of decreased density were interpreted as evidence of gas in the fetal circulatory system, indicating death of the fetus. Re examination in the right lateral projection two days later showed that these areas had increased slightly in extent. At necropsy, the presence of gas in the heart, liver, retro peritoneal tissue and umbilical cord was confirmed.

SKELETAL SYSTEM

Stress fracture

The diagnosis of stress, insufficiency, exhaustion or fatigue fracture is essentially a radiological one. Apart from the march fractures of the metatarsals, the lesion was at one time seldom seen in Great Britain, but reports of cases indicate that it is becoming increasingly more common. Two factors probably explain the increase in its incidence: (1) fatigue brought on by prolonged and unaccustomed muscular activity in young individuals who, up to a comparatively short time before, were as a routine engaged in relatively inactive pursuits, and (2) the greater facilities now available for its radiological recognition.

Stress fracture may be a partial or a complete fracture. It occurs in apparently normal bone, in individuals who show no evidence of associated systemic disease and who give no history of direct trauma. The cause of the condition is not clear. It appears to be one of local inadequacy of metabolism, causing localized skeletal changes which render the bone more pliable and therefore more prone to fracture. Hartley regards it as a gradual yielding of the trabecular structure of the bone under repeated stress, analogous to the exhaustion of the crystalline pattern of metals under overstrain.

The condition is usually unilateral but may be bilateral. The bones most frequently affected are any of the metatarsals except the first, the tibia at a point 2-3 inches below the knee, the upper or lower third of the fibula, the femur a few inches above the knee, the femoral neck, the calcaneum (Hullinger), and the pelvis. In the foot, the second metatarsal bone is most commonly affected, and predisposing factors are the fatigue brought on by prolonged and unaccustomed exercise, causing a weakness of the transverse metatarsal arch of the foot, and congenital shortening of the first metatarsal bone, which throws additional weight on the second metatarsal. Other predisposing factors are an increase in weight bearing on the foot, and badly fitting boots.

Clinically, stress fracture is characterized by chronic pain in the foot or leg, which is relieved by rest and which returns if weight bearing is resumed. When the affected bone is superficial, for example the tibia and metatarsals, there may be some thickening and oedema. If the individual continues his activities untreated, the fracture may suddenly become complete.

There may be no radiographic evidence of the condition for 2-3 weeks, and when the lesion is suspected x ray examination must be carried out at weekly intervals for a month after the onset of pain. The typical x ray appearance is that of a localized cortical callus formation, with a fine hair like crack in the cortex, although in some cases the crack may not be seen. With adequate rest, the callus undergoes rapid organization and a sclerotic zone forms at the site of fracture, so that the bone is ultimately stronger and thicker than it was before. If strain persists for too long a period after the stage of bone fatigue, a transverse area of porosis may develop at the site of fracture. In these cases, recovery may be slow and the risk of complete fracture is increased.

It is important to bear the condition in mind in young adults for, during the process of cortical reaction, the radiographic appearances may give rise to a mistaken diagnosis. The most important of which is osteogenic sarcoma. The presence of the fine hair like crack provides the clue to the diagnosis. Incorrect diagnosis may lead to an unnecessary operation for suspected bone infection or malignancy. The correct treatment of stress fracture invariably leads to recovery.

Air arthrography

Air arthrography is of considerable value for the more precise diagnosis of lesions

of the semilunar cartilage. It is a simple painless method of examination. After the skin and capsule have been infiltrated with Novocain (procaine hydrochloride), the suprapatellar pouch is punctured half an inch above and lateral to the patella, and air is injected with a 20 cubic centimetre syringe attached to the needle by a three-way adapter. Any fluid present is aspirated. The amount of air used varies from 70 to 140 cubic centimetres. The injection is continued until the patient experiences a tight feeling and there is sufficient tension to blow back slowly the piston of the syringe. The needle is then withdrawn and the puncture is sealed. Air-leaks through the puncture on withdrawing the needle are obviated by introducing the needle obliquely and by maintaining pressure on the puncture site with a finger for 2-3 minutes after withdrawing the needle. A firm bandage is applied to the suprapatellar bursa, starting from above, in order to ensure that the air in the knee joint is under pressure.

Cullen and Chance have distinguished five types of lesion as follows: (1) separation of the cartilage from the lateral ligament; (2) separation of the cartilage from the tibia; (3) fracture of the cartilage; (4) fracture of the cartilage with displacement of a fragment; (5) fracture of the cartilage with fragmentation, approaching in some cases almost complete disappearance.

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TROPICAL MEDICINE

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MALARIA

It is not too much to say that the success of the campaigns of the Allies in the Far Eastern Area and in tropical parts of Africa was entirely dependent on the control of the nearly universally prevalent and malignant forms of malaria. Much valuable information on the efficiency of various methods of control has now accrued

Control of infection through mosquito bites

Under military conditions, the destruction of the larvae of carriers and the killing of adult insects in houses by the use of sprays is usually impracticable when the Forces are on the move. At fixed bases more may be done, as shown by Butler in a report from a South Pacific area, where a yearly malarial rate of 2,645 cases per 1,000 men per annum in April 1942 was reduced to 130 per 1,000 a year later by the usual methods of mosquito control. The number of infections in native carriers was reduced by means of mass mepacrine (Atebrin) therapy. On the Gold Coast of West Africa, Eddey found pyrethrum kerosene and pyrethrum aerosol to be the most effective agents, and the cost of either, inclusive of labour, worked out at a small fraction over six pounds sterling for 1,000 units of 1,000 cubic feet, or about sixpence-halfpenny per house monthly. In spite of the increased rainfall, favouring the spread of the disease, in 1943 the malarial incidence was reduced by 34-43 per cent of the 1942 rate. The use of the new and powerful insecticide, DDT (dichlorodiphenyl trichlorethane) in malarial control is discussed by Buxton. Used by itself as a dust, this largely insoluble powder is not of much use against anopheles larvae, but it is of immense practical value in larvicidal oils, for its addition reduces the amount of suitable oil required from 10-20 gallons to less than 1 gallon per acre of water. Working with 5 per cent of pure DDT in diesel oil, Buxton found that an application of 0.1 cubic centimetre per square yard retained its lethal effect against larvae for a period of four days. Owing to the war shortage of pyrethrum, the discovery of DDT is most opportune and its effect in the form of a spray in destroying mosquitoes in houses is more lasting than is that of the older preparation, for there is evidence that its use in concentrations of 100 milligrams per square foot greatly reduces the number of mosquitoes for two or three months after a single spraying, as compared with only one week when pyrethrum is used. Mosquitoes resting on a treated wall will be killed, although not immediately, but even if they have bitten a malarious subject they will not live to infect another. The method may, however, fail in the case of anopheles which fly in and out of the houses without resting on the walls within them, these include *Anopheles punctulatus* and *Anopheles maculatus*.

Control of malaria by the use of drugs

In view of the fact that nine tenths of the world supplies of quinine had fallen into the hands of the Japanese with their capture of the Dutch East Indian Islands, it was providential that German scientists had already discovered at least as effectual a remedy in Atebrin, known in Great Britain as mepacrine hydrochloride and in the United States of America as quinacrine. As neither mepacrine nor quinine is a true prophylactic against malarial infection through the bites of infected anopheles, the drug used had to be given continuously to the members of military forces fighting in Burma and such highly malarious areas as New Guinea and other areas in the East in order to suppress the fever and other symptoms of malaria and to preserve the fighting efficiency of the troops engaged. The evidence given in a Memorandum of the Medical Research Council Committee on Malaria shows that mepacrine is quite safe

and is more effective than is quinine in severe malignant tertian infections. It is tasteless, does not produce any symptoms akin to those of cinchonism and is less likely to be followed by blackwater fever. Neither drug will prevent the common relapses of benign tertian malaria.

The importance of the suppressive action of these drugs is shown by the fact that in the early part of the New Guinea campaign 80 per cent of the Australian troops were laid low by malaria. An intensive investigation to discover the best way of reducing this crippling loss of manpower was organized under the direction of Fairley, the results of which he has recorded. Many Australian and American soldiers volunteered to be infected through the bites of anopheles, and various methods of administration and dosage of both quinine and mepacrine hydrochloride were tested. The results showed that quinine, even in doses of 10 grains daily, was less effective than was 0.1 gramme daily of mepacrine hydrochloride in suppressing malaria attacks and in keeping the men fit for fighting for months on end. In the case of the more serious and deadly malignant tertian malaria the drug was also curative; in benign tertian cases fever is liable to occur when administration of the drug is omitted. It prevented all fatalities from malaria and also eliminated attacks of blackwater fever. The adoption of this line of suppressive treatment in New Guinea reduced the hospital admission rate of malaria from 740 per 1,000 men per annum in December 1943 to 26 per 1,000 per annum in November 1944. Its use, therefore, enabled the campaign to be brought to a successful conclusion.

KALA-AZAR

Control

Burke reports on an experience of 3,489 cases on Assam tea estates during the period 1935-1943. In order to control the disease on fourteen tea estates, of an average population of 26,000, under his care, he relied on frequent mass surveys for the early detection of cases and for their isolation and treatment. Eighty per cent of the total number of cases were treated with Neostibosan and only 190 patients (5.4 per cent) died of intercurrent affections or failure to respond to treatment. In serious outbreaks the infected lines may have to be burnt and, so as to control the sandfly carrier, areas around the coolie lines should be cleared. These measures have proved to be successful in controlling the disease in crowded potential reservoirs of infection; the cases were kept down to the low average of 35.5 per annum.

Treatment

In advanced cases with severe secondary anaemia and epistaxis and other forms of haemorrhage so common in this disease, Cole in East Africa has successfully used continuous drip transfusions of one pint of blood until the haemoglobin rises to at least 50 per cent. In the infantile form of kala-azar in Algeria, Sarrouy and Gillot report very favourably on the use of the methyl-glucamine salt of *p*-aminophenylstibonic acid (Pentastib). The relatively large dose of 0.07 gramme per kilogram of body weight was injected intramuscularly on four consecutive days, or 0.1 gramme per kilogram was injected on three days running. An immediate response was seen in the form of a rapid fall of temperature, disappearance of the parasites and improvement in the blood. Some nausea or sickness may occur, but the reactions are much less when the drug can be injected intravenously.

Leishmaniasis, cutaneous

In areas where oriental sore is very common and disfiguring, it has long been the custom to inoculate the disease at selected unexposed sites, with resulting immunity. Berberian used the method on volunteers, who were reinoculated at various intervals in order to ascertain how soon immunity was produced. It appeared that when the first sore had lasted only for from 123 to 230 days, a second inoculation was effective in producing another sore. After 242-300 days the second inoculation did not produce sores.

TYPHUS

Distribution and epidemiology

Outbreaks of epidemic louse-borne typhus were reported in 1943 and 1944 in Europe and in Egypt. A serious epidemic originated after the occupation of Naples.

winter of 1943-1944 and was remarkable for the effective prophylaxis achieved by means of D D T, the use of which has been reported on by Buxton. This is a non volatile white crystalline substance which has a strongly lethal action on many forms of insects. It may be dusted on the skin, and garments impregnated with it remain fatal to lice for several weeks and after several washes with hot water and soap. In Naples, the powder was dusted by hand blowers up the sleeves and trousers and down the necks of as many as 73,000 persons in one day, with the apparent result that the epidemic was quenched in midwinter, which is the most favourable time for its spread. This important discovery promises to allow the control of post war typhus epidemics, which proved to be so disastrous, especially in Russia, after World War I. The methods in use are quite safe and are unirritating to the skin of treated persons. They proved to be practicable under the disadvantageous conditions prevailing in overcrowded air raid shelters in the Naples outbreak. In Egypt, Kamal and Messih report the prevalence of typhus among the labour forces employed from November to May on war work, with a rapid fall as the temperature rose in June, the disease spread to Upper Egypt, and there were ten times as many cases as there had been in pre war years. No form of treatment availed. In Spain, Urrea reported an outbreak in 1944 in which the use of an intravenous injection of 250-500 cubic centimetres of a solution containing 0.5 gramme of chlorine and 6.5 grammes of sodium chloride in 1,000 cubic centimetres of water was said to be effective. Investigations on the mode of infection of typhus are reported on by Pshenichnov from Russia. Laboratory bred lice were infected by allowing them to feed on patients with typhus and no hereditary louse transmission could be demonstrated. The natural infection from lice through faeces was shown by successful feeding on skins smeared with such lice faeces. If infected lice faeces are kept in an incubator under humid conditions the virus dies out in two or three hours but in dried faeces the virus survives for from five to twenty days. It also survives longer at low temperatures and during winter frosts than it does during the five hot months. Fingernails infected with lice faeces may, through scratching, cause infection. The causative rickettsiae may survive for a long time in dead lice and in their faeces on clothes and may restart the infection.

Diagnosis

In Egypt, Kamal and Messih found that the intradermal injection of 0.2 cubic centimetre of a 25 hour culture of *Proteus OX 19* in 20 cubic centimetres of saline produces an indurated erythema within twelve or sixteen hours in healthy persons, but that it is negative in typhus patients, it is therefore of diagnostic value.

Vaccines

In the United States of America, Topping has confirmed the value of typhus vaccines in causing infected laboratory workers to suffer mild attacks, if any, and as rickettsiae could not be isolated from them the conclusion is reached that the modification of the disease may interrupt the louse man louse chain of infection and serve to control the epidemics of the disease. Wohlrab and Patzer have obtained similar results. In Lenin grad Tokarevich and Epstein found that the vaccine was effective after one year in greatly reducing the severity of any typhus cases that occurred among laboratory workers greatly exposed to infection none of whom died of the disease.

Treatment

The use of antityphus horse serum is reported on by Wolman with 8 deaths in 220 treated cases (3.6 per cent) and 24 deaths in 220 untreated (10.9 per cent). Two 20 cubic centimetre doses were given subcutaneously on the first day and the same dose was repeated once on each of the two following days. The serum should not be given intravenously.

Penicillin is reported by Moragues and his colleagues to prohibit the growth of murine rickettsiae in yolk sac cultures and completely to protect mice injected intraperitoneally with penicillin seven hours after infection with the disease. All the control animals died. On the other hand the United States Army Medical Department Bulletin records that maximum dosage of penicillin had no effect on the course of scrub or of mite typhus in the South Pacific war area.

centimetre of cerebrospinal fluid only one patient relapsed, but in 16 per cent of more advanced cases little or no benefit was obtained

PLAGUE

Epidemiology

In California, Meyer and his colleagues have reported that they have found ground squirrels infected with latent plague, without active symptoms, in July and August. In Mexico, Blanc and Baltazard found the flea *Pulex irritans*, in houses infected with plague, to be harbouring plague bacilli.

Treatment

In Brazil, de Villafane Lastra and Rodeiro had a mortality in bacteriologically proved plague cases under serum treatment of 70.87 per cent, but in thirty-nine cases treated with sulphathiazole in 10 grammes doses daily, the mortality was 23.33 per cent, if four moribund patients were excluded, it was only 14.28 per cent. At Poona in India, Wagle treated 180 cases, the mortality rate under sulphadiazine therapy was 12 per cent and under sulphathiazole therapy was 21 per cent when moribund patients who died within twenty-four hours were excluded. In septicaemic cases when the same drugs were used the mortality rates were 20 per cent and 37 per cent, respectively, as against 91 per cent with iodine treatment.

RELAPSING FEVER

In experimental treatment of small animals infected with relapsing fever and with other pathogenic spirochaetes, penicillin has given promising results. Heilman and Herrell produced in mice "overwhelming" infections with *Spirochaeta (Borrelia) novyi* and saved 25 out of 26 of them by means of penicillin injections, whereas of 28 untreated controls 21 died of spirochaetosis. Hawking likewise fed mice infected with *Spirochaeta (Borrelia) recurrentis* on a wet diet containing 1.5 per cent of sulphapyridine or sulphathiazole, with the result either that infection was entirely suppressed or that its intensity was much diminished. Employment of other sulphonamides was not successful against this infection. Conge and Boyer report on the cure of all guinea-pigs infected with the *Spirillum minus* of sodoku (rat bite fever) even when they were *in extremis*, by daily oral doses of sulphanilamide and other sulphonamide drugs. Lourie and Collier record the rapid disappearance of pathogenic spirochaetes from the blood of mice injected with the calcium penicillin. The best results were obtained with an aggregate of 100 units given in a series of fractional doses.

AMOEBIASIS

During the war period amoebiasis has assumed a position of greater importance than it had for some time past. Payne reports that at base hospitals in Eastern India 51.56 per cent of the total number of dysentery cases were proved to be amoebic in origin, and 33.36 per cent bacillary, 11.13 per cent were of clinical dysentery of undetermined origin. He points out that, contrary to some pre-war estimates, these data prove amoebic dysentery to be one and a half times more numerous than the bacillary forms. Moreover, the duration of the stay in hospital of the amoebic patients varied between 3 weeks and 6 months, usually 28 days, as against 7-14 days, usually 8 days, in bacillary cases. Extensive ulceration verified by sigmoidoscopy, without diarrhoea, and typhilitis—but in no case appendicitis—were frequently met with, together with dyspeptic symptoms in chronic cases. In 50 per cent of the cases mild hepatitis was present, which is thus a part of the disease. Only 3 per cent of 1,000 amoebic dysentery cases went on to liver abscess formation, and 27 (6.69 per cent) of liver abscess cases occurred. All but one patient, who had a secondary staphylococcus infection, was covered under the emetine and aspiration method of treatment. In 50 per cent of amoebic dysentery cases clinical cure was effected by means of emetine injections and with carbarsone given orally. Inadequate treatment of the first attack predisposes to relapse.

Men with relapsing amoebic dysentery who have been invalided home from Burma have proved to be especially resistant to treatment. Adams records that in his long experience of chronic relapsing amoebic dysentery cases in a Liverpool hospital, emetine in its various forms remains the sheet anchor in treatment, it should, however, be supplemented by other drugs. Until recently in many hundreds of cases only one

had failed to respond to the treatment here described, although the course may have to be repeated if relapses occur. A few injections of emetine are followed, if required, by the use of emetine bismuth iodide (best given in easily dissolved soft gelatin capsules), emetine periodide and auramine. Stovarsol and carbarsone are also of use but Yatren (chiniofon) and bismuth are of doubtful value. After an attack has been arrested by means of emetine injections, a course of one or more of the other drugs should be given orally for three weeks. Recently, of emaciated patients from Burma most have been cured and others greatly benefited by this treatment, but some required repetition of the course.

Amoebic hepatitis and liver abscess

Sodeman and Lewis report on seventy-eight cases treated with 1 grain doses of emetine hydrochloride daily for from six to twelve days with early clinical improvement and no mortality. The method of treating amoebic abscesses of the liver by means of aspiration of the pus and by giving intramuscular emetine injections has reduced the case mortality from over 50 per cent to 5-14 per cent. Noth and Hirshfeld record the successful treatment of an amoebic liver abscess, complicated by secondary infection from *Streptococcus pyogenes* group C, by the introduction of penicillin into the cavity through a fixed catheter, every four hours up to fifteen hours, with sterilization of the abscess cavity.

BACILLARY DYSENTERY

Arthritis

After bacillary dysentery arthritis is often a very troublesome complication. Bonnin and Kay report having cultivated *Shigella paradysenteriae* (Flexner) from rectal swabs in four out of five such cases, and they obtained good results in treatment by means of a single course of sulphaguanidine, total dosage 120-126 grammes.

Treatment

Yet another sulphonamide preparation, phthalylsulphathiazole, which closely resembles succinylsulphathiazole (Sulphasuxidine), is recommended by Poth and Ross in 3-6 daily doses totalling 0.0625 to 0.249 gramme per kilogram of body weight, as being the best of this group of drugs. Phthalylsulphathiazole also proved to be of value in 6 cases of chronic ulcerative colitis and as a preparation for operations on the bowel, on account of the great reduction it causes in *Bacillus (Escherichia) coli*.

Phage treatment of bacillary dysentery has sometimes been advised on the strength of its general use without controls. Boyd and Portnoy record a carefully controlled trial of this treatment in the case of German prisoners, using a German preparation captured in North Africa. They found a difference too small to be of significance in its prophylactic use, but in a treated group the incidence of bowel trouble was greater than it was in the control series during the same period of its use.

FILARIASIS

Incidence in the South Pacific

Michael reports on the frequent occurrence of *Wuchereria bancrofti* among American personnel serving in the South Pacific area, who manifested clinical symptoms of infestation after from seven to nine months' exposure. The progress of the disease was marked by repeated attacks of fever, accompanied by the appearance of painful, swollen and red areas in the extremities. The great majority of the patients had funiculitis, epididymitis, orchitis or hydrocele. If removed glands are left for many hours in physiological saline at 37° C., living filaria may be found emerging from the cut surfaces. Spontaneous recovery usually follows the departure of the patient from the endemic area. The United States Naval Bulletin reports on two unpublished papers dealing with this disease in the South Pacific. About one-fifth of the number of soldiers employed there showed symptoms attributable to filariasis. The onset of symptoms may occur as early as three months after arrival. Pain, swelling and redness due to lymphangitis appear in the arm in 38 per cent, in the leg in 14 per cent and in the scrotum in 56 per cent of the cases. Eosinophilia was found in about two-thirds of the number of patients; Fairley's intradermal test was positive in 90.8 per cent of the infected but in

only 10.5 per cent of control persons who had never lived in the Tropics. Mapharsen and sulphathiazole are useless in treatment.

SCHISTOSOMIASIS

Diagnosis

Pifano and Mayer point out that comparatively few trials of Fairley's intradermal diagnostic test for schistosomiasis have been carried out in the case of *Schistosoma mansoni* infections. They have obtained positive reactions as early as the third week after contact with infested waters. Of established cases, 97.3 per cent gave evidence of antibodies. Of possible latent cases, without the presence of eggs in the faeces, 40 per cent reacted to the test. Intense positive reactions were always obtained in advanced bilharzial cirrhosis and in atrophy of the liver with splenomegaly—although in such cases ova are difficult to find in the stools—so in these the test is of great practical value. Ottolina and Atencio are dissatisfied with the usual laboratory methods of diagnosing this disease. They advise removing a small fragment of the liver by means of a trocar and syringe, and digesting it in 4 per cent potassium hydroxide at 60–80° C., by this means they found bilharzia ova in 18 (45 per cent) of livers examined.

TROPICAL ULCER

Tropical (phagedaenic) ulcer

Tropical ulcer is often a source of major disability in persons living in hot humid areas such as Burma, Malaya and the South Pacific, because it is often chronic and is difficult to cure. Forrest reports excellent results from the use in indolent tropical ulcers of 0.1 per cent Propamidine in a basis of Lanette wax or of hard paraffin or in a water-soluble jelly, there was apparent cure in ten days or less after the failure of the local application of sulphathiazole. The ulcer was filled with the preparation and was covered with a single layer of gauze and an Elastoplast bandage, the dressings were changed every twenty four or forty eight hours. In a large experience in Assam, where this affection is especially common, Pattanayak found in early sloughing cases the local application of powdered sulphanilamide, which is cheap, or of sulphapyridine, which is costly, to be the most effective treatment. In chronic indolent cases he prefers to use solutions of copper sulphate.

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RECENT DEVELOPMENTS IN PHARMACOLOGY AND THERAPEUTICS

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During the past year advances have been made in many directions in our knowledge of the actions and uses of drugs. Naturally a considerable amount of attention has been paid to antibacterial substances but other remedies have not been neglected. It is probable that as a result of the cessation of war and of the great strides made by the organic chemists many new drugs will appear. It is of the utmost importance for the rational and satisfactory development of therapeutics that the value of each new preparation should be assessed as accurately as possible before it is made available for use by general practitioners, who usually have neither the time nor the facilities for making this assessment. In this connexion attention is drawn to an important paper by Green on the clinical evaluation of new remedies in Great Britain. He gives an outline of the work of the Therapeutic Trials Committee and after a brief but clear discussion emphasizes the advantages of having an impartial body of medical experts to organize the clinical testing of promising new remedies of academic or commercial origin. It is good to read that the aim of the Medical Research Council is to ensure that the doctor at the bedside has every opportunity of deciding the clinical value of every new remedy in the most effective and expeditious way.

SEVENTH ADDENDUM TO THE BRITISH PHARMACOPOEIA 1932

The Seventh Addendum to the British Pharmacopoeia 1932 came into official use on 1st February 1945. In its recognition is given to a number of important drugs and preparations.

New pharmacopoeial names

Amethocaine hydrochloride—*p*-Butylaminobenzoyldimethyl-amino-ethanol hydrochloride (Butethanol, Decicain or Pantocaine). This is allied pharmacologically to procaine and is used in 2 per cent solution for surface anaesthesia and in 0.5–1 per cent for spinal anaesthesia and as a 1 in 1,000 solution for infiltration anaesthesia. In order to reduce absorption it should always be mixed with adrenaline.

Amphetamine—This is a mixture of racemic desoxy nor ephedrine bases, known by the trade name Benzedrine. It has sympatheticomimetic activity differing from adrenaline in its more marked stimulating effect on the cortical centres. It has been used in inhalants for the relief of acute coryza and orally in the form of the sulphate in the treatment of narcolepsy and allied conditions. It is only slightly soluble in water but amphetamine sulphate is readily soluble.

Soluble pentobarbitone—Sodium ethylmethyl butylbarbiturate (Nembutal) is one of the more quickly acting barbiturates.

Soluble thiopentone—A mixture of ethyl (1-methylbutyl)-thiobarbituric acid with sodium carbonate commonly known as Pentothal sodium is one of the most rapidly acting barbiturates of great value as a basal anaesthetic. Its use is not without risks, which have been analysed in a *Lancet* Annotation.² They may be briefly summarized as (1) danger of overdose especially in patients who are shocked or gravely ill, (2) injection into an artery, which is heralded by an intense scalding pain and may be followed by such serious results as will necessitate amputation of fingers or arm, (3) painful indolent sloughing after subcutaneous injection of strong solutions. The tissue reactions which ensue on inadvertent subcutaneous injection in rabbits can be pre-

vented by immediately infiltrating the area with 1 per cent procaine (Elder and Harrison).

Sulphonamides.—Sulphacetamide (commonly known as Albucid), sulphapyridine, sulphathiazole and sulphadiazine have become official preparations.

Theophylline with ethylenediamine (Euphyllin, Cardophyllin, aminophylline).—This has been used as a diuretic particularly in cardiac oedema and is of value in cardiac asthma and when there is breathing of the Cheyne-Stokes type. The drug acts probably by increasing the blood flow through the coronary circulation. It is said to have an antispasmodic effect on smooth muscle.

PENICILLIN

Since the present volume contains a special article on penicillin (see p. 74) none of the subjects discussed therein is dealt with in this place.

OTHER ANTIBIOTICS

Of the other antibiotics which have been used in therapeutic trials one must record the failure of patulin to maintain its reputation in the treatment of the common cold (Stansfield, Francis and Stuart-Harris; Report, Patulin Clinical Trials Committee). Reports are now available of gramicidin S, a crystalline polypeptide which was introduced in the U.S.S.R. (Gause and Brazhnikova). Sergiev has found that a characteristic feature of its local application in the form of solution or ointment is the alleviation of pain. Patients with infections of the skin, suppuration of soft tissues, empyema and peritonitis have been successfully treated with this substance.

THE SULPHONAMIDES

Toxicity

The toxic manifestations of the sulphonamides are well known, but the why and the wherefore are in many instances not well understood. There is some relationship to the blood concentration of the drug and the duration of treatment, but these are by no means the sole factors. During the past year some work has been done which seems to be of help in dealing with those patients who are sensitive to this group of drugs. Park has divided the so-called allergic phenomena into two groups, as follows: group (1) those which occur when the drug is given internally and results in fever and in morbilliform and other skin rashes, and group (2) those which occur when the drug is applied to the skin and produces an eczematous dermatitis. For desensitization 0.1 gramme of the drug is given on the first day and the dose is doubled each succeeding day until, in four or five days' time, 1 gramme is reached. It may be necessary to start with a dose much smaller than 0.1 gramme (in one instance it was 0.005 gramme). For the patients with dermatitis it is usual to commence with 0.02 gramme and proceed in the same way. Tate and Klorfajn who discuss the underlying chemical basis of sensitization and desensitization recommend a similar method. Rosenak and Maschmeyer give the clinical and pathological findings in the case of a patient with periarteritis nodosa possibly due to sulphadiazine hypersensitivity. Peterkin found that in six out of sixty-five cases of light eruption due to external application of sulphonamide powders, the drug concerned was sulphanilamide. He suggests that inhalation of the powder sensitizes the patient to the drug, and urges that powdered sulphonamide compounds should not be applied to the skin for minor ailments. Of more than 200 cases treated in North Africa with 5 per cent sulphathiazole in Lassar's paste or Lanette wax cream and freely exposed to the light, in only one there developed a mild and rapidly subsiding skin eruption. As a result Peterkin considers that this treatment is as safe as that using white precipitate ointment. Abramowitz, however, is against the indiscriminate use of any sulphonamide ointment since complications such as dermatitis and photosensitization render the patient sensitive to the subsequent use of the drug.

Local application of sulphanilamide produces more than 50 per cent inhibition of bone phosphatase activity, whereas sulphathiazole applied locally has little such effect (Blum). It is suggested that the former drug should not be used as a local application at the site of fracture (Silver and Golding).

Dowling and Lepper studied the incidence of drug fever accompanying second courses of sulphonamides given to patients who did not have a febrile reaction during

the first course Of 144 patients who received a second course of the same sulphonamide, in sixteen (11.1 per cent) drug fever developed, whereas of 169 patients whose second course consisted of a different preparation, only six (3.6 per cent) had a febrile reaction The authors conclude that when a second course of sulphonamides must be given another compound should be used

Murphy and others differentiate three chief types of damage to the renal parenchyma, as follows (1) toxic effects due to obstruction, (2) extensive tubular degeneration with necrosis of pyramids and (3) extensive glomerular involvement in addition to wide spread tubular injury The first type is the commonest, being due to low volume and insufficient alkalinity of the urine Ohnysty and Wolfson recommend the administration of at least 4 pints of fluid daily and of an initial dose of 8 grammes of potassium bicarbonate followed by 2 grammes every four hours The potassium salt which aids diuresis is well tolerated except in severe renal impairment or adrenocortical insufficiency Rohr and Christopher have found that in patients receiving sulphadiazine after operation an intravenous injection of 1 litre of $\frac{1}{2}$ molar sodium lactate was effective in maintaining urinary alkalinity for about 24 hours After intravenous therapy was discontinued 24 grammes of sodium bicarbonate given daily *per os* were found to be necessary The authors note that sodium sulphadiazine should not be mixed or come in contact with the lactate solution in the intravenous set

As regards blood dyscrasias due to sulphonamides, experimental work on rats suggests that folic acid—a constituent of crude liver preparations—may be of value in preventing or treating agranulocytosis (Axelrod and others, Goldsmith and others) Sherlock and White report that the first sign of toxic purpura is nearly always epistaxis and that this manifestation is an indication for the immediate stopping of administration of the drug and the giving of a blood transfusion Acute macrocytic haemolytic anaemia has been reported as occurring after the administration of 39 grammes of sulphadiazine over a period of nine days to a patient with atypical pneumonia recovery coincided with the institution of liver therapy (Layne and Schemm)

The newer sulphonamides

Sulphadimethylpyrimidine (Sulphamezathine) is quickly absorbed but owing to its rapid excretion it is impossible to maintain a high blood level unless full doses are given frequently A large proportion of the drug is quickly acetylated and thus is rendered inactive The concentration in the cerebrospinal fluid rarely exceeds half of that reached in the blood (Kremer, Phillips and Stanier) Toxic effects, especially renal symptoms are rare and are not serious so that Sulphamezathine would appear to be one of the least harmful of the sulphonamides and to be well tolerated Good results have been recorded with its use in the treatment of lobar pneumonia (Ramsay and his co workers) Sulphamonomethylpyrimidine (Sulphamerazine) is more quickly absorbed than is sulphadiazine and is more slowly excreted than is Sulphamezathine, so that it is possible to attain a high blood concentration more quickly with it than with the former drug and to maintain it for longer than can be achieved with the latter drug (Leading Article²) Indeed an adequate level may be maintained by lower and less frequent dosage of Sulphamerazine than is essential with the other two (Hawking) Welch and his co workers indicate that this makes Sulphamerazine particularly suitable for use as a prophylactic when it is desired to maintain a certain concentration in the blood over a long period Oliver and Anderson obtained excellent results in the treatment of fifty six patients with meningococcal meningitis and other workers have reported that in other infections Sulphamerazine is at least as effective as is sulphadiazine (Leading Article¹) Earle finds that the urinary concentration at any given plasma level is less than that of other sulphonamides so that there is less risk of urinary disturbance Dowling and his colleagues, however, in a series of 1,328 patients found that the incidence of renal calculi was greater and of drug fever at least as great with Sulphamerazine as with sulphadiazine They conclude that at the present time sulphadiazine is the drug of choice for systemic sulphonamide therapy

Marfanil (*p*-aminomethylbenzene sulphonamide) has the amino group separated from the benzene ring by a methyl group so that it is not diazotizable and cannot be estimated by Marshall's method (Hawking) It is not inhibited by *p*-aminobenzoic acid Mitchell Rees and Robinson found it to be of great value in the local treatment of war wounds

For the production of an antiseptic effect in the intestine, succinylsulphathiazole (Sulphasuxidine) and phthalylsulphathiazole (Sulphaphthalidine) appear likely to be more effective than sulphaguanidine. Both are poorly absorbed, only about 5 per cent appearing in the urine and the blood concentration not exceeding 1.5 milligrams per cent (Poth and Ross). Measured by the ability to suppress the growth of coliform organisms, the phthalyl compound is at least twice as powerful as is the other. Sulphaphthalidine has proved to be useful in the treatment of ulcerative colitis by reducing diarrhoea, intestinal haemorrhage and the symptoms of toxæmia (Bargen). In the treatment of operation wounds, Sulphasuxidine administered orally combined with local application of sulphathiazole has led to greatly improved results in the closure of colonic stoma (Dixon and Benson).

Administration

In view of the necessity which will arise of administering sulphonamides to patients with active malaria, it is comforting to learn that sulphathiazole can be combined with quinine or mepacrine therapy without an increased incidence of unfavourable reactions except possibly vomiting (Harned and Etteldorf). Peterson and Finland find that procaine in amounts ordinarily employed for local anaesthesia may be absorbed into the circulation in concentration sufficient to inhibit the bacteriostatic effect of the sulphonamides. They think it desirable to avoid procaine and other *p*-aminobenzoic acid derivatives for infiltration when performing exploratory punctures of potentially infected areas.

Mutch has made an important contribution on the inhalation of chemotherapeutic substances. Various methods are described and quantitative details are given of the fate of two sulphonamides inhaled as mists from their aqueous solutions. It would appear that normal subjects may absorb about 1 cubic centimetre of the original solution per hour and that bronchiectatic subjects absorb rather more. This form of therapy has been employed by Appelbaum in the treatment of various types of bronchial infection, with distinct improvement in forty-three out of fifty cases. A 5 per cent solution of sodium sulphadiazine was used in the nebulizer with an oxygen flow of 4 litres per minute.

Waud reports some interesting work on the absorption of sulphathiazole from wounds. It would appear that in tissues more than 2–3 millimetres below the surface of the wound, the concentration of sulphonamide is less when the drug is applied locally than when it is given by the mouth. The nature of the vehicle in which sulphathiazole is suspended influences its diffusion. When a water-soluble base or an oil in water emulsion is used the absorption of the sulphonamide takes place quite readily but when it is incorporated in a fatty or paraffin base little of the drug actually reaches the tissues. When it is suspended in a liquid oil the sulphathiazole is deposited in almost pure state on the surface of the wound or of the dressing. Other things being equal, the higher the percentage of drug in the base the greater its concentration in the tissues. From these and other results it seems clear that whenever infection has spread below the surface it is advisable to combine local application of the drug with oral administration which itself can produce in the wound fluids a concentration of drug that is not negligible (Sager and Pudenz).

Intraperitoneal administration of sulphonamides has been reported on favourably by various surgeons (Stafford, Beswick and Deeb). Gardiner believes that sulphapyridine is the drug of choice and uses 15 grammes of the sterilized powder. Chesterman has had good results with microcrystalline sulphathiazole. Ogilvie, however, disapproves of these since, being relatively insoluble and irritant, they are liable to produce small abscesses: he prefers sulphadiazine. Giblin used 10 grammes of sulphadiazine suspended in 100 cubic centimetres of saline, which he injected through a separate catheter into the abdominal cavity.

Dosage

Alstad finds that in patients with pneumonic disorders blood concentration varies with the amount of drug administered, the larger dose producing the higher blood level. Six grammes of a sulphonamide daily given at four-hour intervals maintains in most cases an adequate concentration at which bacteraemia is readily controlled, mortality is low and the risks of leucopenia are negligible. Dick, from a careful study of 161 patients concludes, however, that sulphapyridine blood levels cannot be corre-

lated with duration of primary pyrexia, the incidence of complications and the final outcome of the disease. Clearly prognosis in pneumonia depends upon more than the administration of a sulphonamide.

Sulphonamides in prophylaxis

The use of sulphanilamide to prevent recurrences of rheumatic infection has been favourably reported on by various workers (Feldt, Dodge, Baldwin and Weber). Slocumb and Polley have reviewed reports on the use of sulphanilamide in 751 patients, 1.6 per cent of those treated had recurrences as compared with 10–45 per cent among the controls. Sulphanilamide is contra-indicated in the treatment of acute rheumatism and is useless in preventing an attack after a throat infection with haemolytic streptococci has become apparent. The drug in doses of 1–3 grammes daily is of value only during the period of its administration. Administration is not free from risk since toxic reactions have been noted in 10–40 per cent of cases, so that leucocyte differential counts and estimations of haemoglobin and blood sulphanilamide should be done at frequent intervals. It is my view that this method of prophylaxis is still under trial and should be left to the large clinics in which there is adequate control.

Pressman and Bender, from their studies on bacteraemia after the extraction of teeth, recommend the administration of a sulphonamide, 1.5 grammes four times during the previous day, 2 grammes four hours before extraction and 1.5 grammes four-hourly for one or two days afterwards in order to obtain maximum protection.

As regards prophylaxis of infections of the upper respiratory tract the evidence is more doubtful. Both Holbrook and Coburn² report excellent results from the use of sulphadiazine. Cecil, Plummer and Smillie believe that symptoms due to secondary bacterial infection are ameliorated but they are opposed to the routine use of sulphonamides in the treatment of the common cold. Hayden and Bigger found that sulphonamide lozenges given as a routine reduced the incidence of slight coughs; they state that the protection against infection is so trifling as to make routine administration of a sulphonamide not worth while. Vollum and Wilson studied the effect of sucking lozenges containing sulphapyridine and sulphathiazole on healthy and convalescent carriers during a scarlet fever epidemic and found that the measure did not have any effect in clearing the infective type of streptococcus from the throat or in preventing streptococcal infection in healthy non-infected contacts. In a Leading Article¹ in the *British Medical Journal* it is stressed that the risks of toxicity and particularly of producing drug resistant strains of bacteria are not negligible. It is concluded that at present sulphonamide prophylaxis may be recommended for the control of outbreaks of meningococcal infection (2 grammes daily for two or three days) and streptococcal infection (1 gramme daily for from three to four weeks).

Sulphonamide resistance in gonococcal infection

Campbell, from his experiences in the North African and Italian campaigns, has the impression that resistant cases are increasing in number. Harkness could obtain no correlation between the laboratory and the clinical findings, and Boroff suggests that in some patients the resistance may be due to an anti-sulphonamide activity of the blood. Frisch, however, found that in many instances gonococci obtained from clinically resistant patients were susceptible *in vitro* to a concentration of 5 milligrams of sulphathiazole per 100 cubic centimetres of culture medium. He believes that the clinical resistance in such cases is due to inadequate dosage, poor penetration of the drug into the infected tissue and obstruction to effective drainage of pus. Schnitker and Lenhoff state that the oral administration of urea (30 grammes daily) with the sulphonamide may be effective in the treatment of patients with gonorrhoea previously resistant to sulphonamides alone.

OTHER SUBSTANCES

Arsenicals

There is still no agreement on the best method of administering arsenicals to patients with early syphilis. Various regimens have been recommended but it is impossible at present to evaluate them since it will require at least ten years before one can begin to determine the real value of any new treatment. Here it must suffice briefly to mention the interim experiences of some of the workers in this important field of medicine.

Eagle's experience with nearly 5,000 patients leads him to believe that injections of Mapharsen three times a week (1 milligram per kilogram of body weight) plus a weekly injection of bismuth salicylate, over a period of between nine and twelve weeks, will effect a cure in 85-90 per cent of early cases. A decrease in either Mapharsen or bismuth to less than these amounts resulted in a greater proportion of treatment failure. Even with the suggested dosage the results were not as good with secondary syphilis as with seropositive primary syphilis. Several reports are available of the five-day therapy. Cannon and his cooperators found that three or four daily injections of 2 per cent arsphenamine with a total dosage of 1.5-4.4 grammes over five or six days produced prompt healing of surface lesions and in 66 per cent of patients whose subsequent history had been followed, led to apparent clinical and serological recovery for periods up to three years; owing, however, to the frequency of reactions—some of which were very severe—Cannon concluded that this routine is dangerous and relatively ineffective. Neilson and his co-workers, using an intravenous drip of Mapharsen over a period of five days, had serious reactions in about 6 per cent of 487 patients and a fatality rate of 0.76 per cent. Craige and Sadusk gave 240 milligrams of Mapharsen in an intravenous drip for twelve hours each day for five days. They claim that with this treatment the patient leaves the hospital in a non-infectious state and almost always remains non-infectious, a very important feature from the standpoint of social medicine. The disadvantage lies in the danger of an occasional severe toxic reaction which rarely may be fatal. Goldblatt gave daily injections of 60 milligrams of Mapharsen in 5 cubic centimetres of sterile distilled water for 30 consecutive days and obtained results comparable to those obtained with other forms of intensive therapy. The United States Public Health Service has published a valuable study based on the experiences of the Cooperating Clinics of the New York and Midwestern Groups (Report). The best results were obtained from the use of multiple injections of Mapharsen combined with typhoid vaccine. The administration of bismuth during the period of treatment appeared to improve the results. Acute encephalopathy was observed in 7.1 per 1,000 treatments; of these 3.2 per 1,000 had a fatal result, the remainder of the patients recovering. Thomas and Wexler believe that fever increases the resistance of the host and has a direct antispireochaetal effect. They used daily injections of 1 milligram of Mapharsen per kilogram of body weight and had four fever sessions over a period of ten days. There was a low incidence of pathological cerebrospinal fluid findings in patients observed for periods up to four years. N. Jones and his colleagues tested various schemes of arsenotherapy combined with fever therapy and found that the best results were obtained without serious complications when 2 milligrams of Mapharsen per kilogram were given in 250 cubic centimetres of 5 per cent glucose and physiological saline at the termination of a five-hour spell of fever at 106° F. The injection was given fairly rapidly and was completed by the time the fever had receded to 105° F.

Toxicity.—Astrachan has reported benefit from the use of crude liver extract in the prevention and relief of toxic manifestations. The extract should be injected fifteen minutes before the administration of the arsenical or heavy metal. McChesney, Barlow and Klinck, investigating the detoxicating action of various organic acids, found that ascorbic acid and *p*-aminobenzoic acid were of value when injected in the same solution as was the arsenical. Experiments indicated that ascorbic acid did not affect the therapeutic efficacy of the arsenic.

New arsenicals.—Phenarsine hydrochloride (dichlorophenarsine hydrochloride) has been tested with satisfactory therapeutic results in 112 patients (Boardman and Kaldeck). There were some minor reactions but in only seven patients out of 112 was it necessary to discontinue administration of the drug. Eagle, Hogan and Fleishman have found that trivalent phenylarsenoxides, when applied to experimental lesions in the rabbit at varying intervals after the inoculation of a suspension of *Treponema pallidum*, were effective in killing the parasites as much as eight hours later, with only slight reaction. This result offers some promise of value in prophylaxis.

Antiseptics

Acridines.—Recently interest has revived in the clinical use of the acridine antiseptics and Poate in a review recommends the use of 5-aminoacridine which is stainless, stable in solution, has a *pH* of 6 and is innocuous to human tissues in a concentration of 1 in 1,000. Its adsorption on cotton is 23 per cent compared with 33 per cent for

non-irritant to the skin and when applied to all the openings of the clothing it is said to give good protection for thirty days after treatment (Annotation¹).

Insulin

The search for the ideal modification continues. Protamine zinc insulin by itself is not the complete answer to the problem. Slow and prolonged in action, it often does not prevent heavy glycosuria after meals and, more important, when it is given in large doses it is very apt to produce severe hypoglycaemia in the early hours of the morning. Reports are now available of the qualities of globin insulin when it is used on a large scale. Eaton¹ believes that the effect of this modification is more nearly physiological than is that of any other single type of insulin. Duration of action varies with the dose and with the severity of the diabetic state. Martin, Simonsen and Hamann state that the effect on the blood sugar begins within an hour of the injection being made, continues slowly for from three to five hours, reaches its peak between the sixth and the eleventh hour and slowly fades until it disappears about the eighteenth hour. All workers remark on the necessity for providing more carbohydrate earlier in the day when globin insulin is substituted for the zinc protamine variety. The majority of out-patients respond well or fairly well to its use. The claim is made of freedom from local reactions, but this may be due to its recent introduction. Mosenthal reports that two patients who were allergic to protamine zinc insulin were not sensitive to globin insulin, but remarks that sooner or later instances will be forthcoming in which the opposite will hold true. As regards its clinical use globin insulin, being a clear fluid, need not be shaken before the syringe is filled, but it must not be combined in the same syringe with protamine zinc insulin. It is recommended that the morning injection be given between three quarters of an hour and one hour before breakfast so as to allow for the lag of onset in the blood sugar response. In transferring a patient from protamine zinc to globin insulin all are agreed that the dose in units should be reduced by a quarter or a third. Since hypoglycaemia is liable to occur about 11 a.m. and especially about 4 p.m., extra carbohydrate may be required just before these hours. As regards the type of patient suitable for globin insulin, Mosenthal believes that alone it is particularly valuable for patients who show postprandial hyperglycaemia but have a fasting blood sugar within normal limits. When morning hyperglycaemia requires protamine zinc insulin which does not adequately control the daytime glycosuria, a separate injection of globin insulin has been found to be of great help. By itself globin insulin is contra-indicated for patients with severe diabetes since it is incapable of covering a sufficiency of carbohydrate and it does not prevent the steady rise of blood sugar which occurs in the early morning hours.

Continued trials are reported of the use of mixtures of soluble insulin and protamine zinc insulin. Lawrence and Oakley suggest for severe diabetics the use of soluble insulin in the morning and a soluble protamine zinc mixture in the evening. In this way postprandial glycosuria is controlled during the day, rise of blood sugar is prevented during the night and morning ketonuria is abolished. This type of treatment proved to be particularly successful in children and in pregnant diabetics. The results of mixing soluble with protamine zinc insulin have been specially studied in the United States and attention is drawn to an excellent paper by Colwell. Protamine zinc insulin mixed with excess of soluble insulin forms a series of precipitates showing more prompt and intense but less prolonged activity than does commercial protamine zinc insulin: the effect on the blood sugar indicates that it is the result of a single complex insulin formed with an action peculiarly its own rather than of two compounds one rapid and one slow in action. The mixture recommended by Colwell contains 250-300 units of insulin with 1 milligram of protamine and 0.2 milligram of zinc. He states that one injection of the mixture in the morning controls postprandial glycosuria efficiently, is less liable to produce hypoglycaemia and does not require supplementary insulin with moderate carbohydrate diets. If for any reason it is found necessary to add soluble insulin this is reflected directly in an increase in the rapidity of effect. Colwell's mixture contains about a third of the protamine and zinc of the standard protamine zinc insulin. MacBryde and Reiss have obtained good results with a modification containing half the protamine and zinc. Some slight experience in the use of similar mixtures leads me to believe that this line of treatment is well worth pursuing, particularly for patients who are often highly intelligent and are well capable of accurately measuring the varying amounts of the different insulins.

Diabetic coma—Notice must be taken of two very important papers based on data from Joslin's Clinic. The essentials of treatment are emphasized and great stress is laid (1) on the need for adequate dosage of insulin as soon as possible, (2) on the necessity of control of further amounts by estimations of blood sugar, (3) on the necessity of combating dehydration by subcutaneous or intravenous administration of saline and (4) on the value of gastric lavage. There is no place for alkali or for any of the so-called cardiac or circulatory stimulants. Both Joslin and Root condemn the administration of glucose in the early stages of treatment and state that this is one of the main reasons for the high rate of mortality in cases of diabetic coma. Although there is some experimental evidence to support the views of these workers, there is little doubt that to the prompt and energetic treatment outlined above is to be attributed the very low mortality of two deaths in 123 cases. It is worth while repeating that success in the treatment of diabetic coma depends upon early diagnosis and the giving of adequate insulin as soon as possible.

Thiouracil

Experimental and clinical observations are consistent with the view that thiouracil prevents the iodization of tyrosine and thus interferes with the synthesis of the thyroid hormone (Franklin, Chaikoff and Lerner, Rose and McConnell). Once thyroxine is present in the body thiouracil cannot prevent its normal effect, as is shown by the therapeutic effect of thyroid hormone in myxoedema even when thiouracil was given synchronously (Dunlop). When the action of thiouracil is sufficiently intense and prolonged to produce a marked decrease in the synthesis of thyroid hormone, the anterior lobe of the hypophysis is stimulated to increased production of the thyrotrophic factor in an attempt to whip up to increased activity the poorly functioning thyroid tissue. The tissue responds by becoming hyperplastic although there is not any effect on the output of hormone (Astwood¹, Leys). Leys has reported on the successful treatment of sixteen hyperthyroid patients with methyl thiouracil which has the same action as thiouracil but is more easily and safely manufactured.

About 15 per cent of the thiouracil is destroyed in the alimentary tract while the remainder is very rapidly absorbed and disseminated through all the tissues and tissue fluids. After a single dose of 0.2 gramme the highest blood concentration (2-3 milligrams) is attained in fifteen minutes, thereafter there is a rapid fall declining to a mere trace in the course of eight hours. When the daily intake amounts to 0.6 gramme in divided doses it takes forty-eight hours for a constant blood level of about 3 milligrams to be achieved. Thiouracil passes into the fetal tissues in the pregnant animal and is found in the thyroid gland. Of the thiouracil absorbed about 40 per cent is destroyed in the tissues, and the remainder, about half of the total amount ingested, is rapidly excreted by the kidneys, twenty-four hours after the last dose only traces can be detected in the urine (Williams, Williams and Clute¹).

Dose—All workers are agreed that the initial dosage should not exceed 0.2 gramme five times daily and generally should be limited to 0.6 gramme in the twenty-four hours. According to Williams this should be continued for two or three weeks and then should be reduced to 0.4 gramme daily until the basal metabolic rate falls to normal limits, when 0.2 gramme should be given daily. After the drug has been administered for a period of two months an attempt should be made to reduce the maintenance dose to the lowest possible level consistent with the patient's wellbeing. A daily dose of 0.1 or 0.05 gramme often suffices (Himsworth) but Eaton² points out that in some cases 0.4 gramme may be required. Astwood² has reported that in nine patients clinical wellbeing with a normal metabolic rate has been maintained for from two to eight months after the cessation of treatment. This suggests that if the patient continues to do well with steadily decreasing doses, administration of thiouracil should be stopped, a view which is strengthened by the fact that untreated thyrotoxicosis has often proved to be a self-limiting disease.

Results of treatment—The drug has proved to be effective in all types of hyperthyroidism—in the primary form, in toxic adenoma or in that type which recurs after partial thyroidectomy. Patients can lead a quiet outdoor life and even do light work during treatment, but rest in bed is advisable at the beginning of the treatment, since it accelerates the response to the drug (Rose and McConnell). The patient with primary thyrotoxicosis may begin to feel more comfortable within a week of commencing her

course of thiouracil but little change can be noticed until the end of the second week. The most marked changes have been noted to occur in the third and fourth weeks (Williams). The first indication is a gradual disappearance of flushing, followed by a reduction of sweating and a diminution of tremor. The weight commences to rise, menstruation improves, palpitation disappears and, generally last of all, the pulse becomes slower. In some patients disorders of cardiac rhythm may yield to administration of thiouracil, but in others quinidine may be required (Rose and McConnell). The degree of lid retraction may be reduced but there is seldom much change in the exophthalmos. The size of the goitre is usually not significantly affected (Himsworth) although in some cases it may become smaller; if an overdose of the drug has been given increase may occur. The basal metabolic rate falls during the first three weeks, generally reaching a normal level within six weeks; the blood cholesterol increases, and carbohydrate and nitrogen metabolism return to normal with a reduction in creatinuria. When the drug is stopped, thyrotoxic manifestations generally reappear within a few weeks, but disappear when treatment is recommenced (Williams and Clute²). Patients with toxic adenoma react more slowly than do the others and it should be remembered that previous treatment with iodine delays the response to thiouracil (Moore and his co-workers). At first it was believed that all hyperthyroid patients responded to thiouracil, but several cases have now been reported to be refractory (Leiter and his co-operators). It is of interest to record the experience of these workers in producing remissions in two patients with thyroid adenocarcinoma and extensive pulmonary and osseous metastases.

The presence of other endocrine disorder generally does not interfere with the action of thiouracil on thyroid hyperactivity. Bartels successfully treated a case of thyrotoxicosis associated with acromegaly, but Astwood² obtained a relatively poor response in two similar patients. The latter worker was successful with a case of thyrotoxicosis and Addison's disease of the suprarenal cortex. Thyrotoxicosis associated with diabetes has been successfully treated by several workers (McGavack and his colleagues; Rose and McConnell; Eaton²). Eaton² has discussed the treatment of the expectant mother suffering from hyperthyroidism. He himself treated two patients and in one case the infant had an enlarged thyroid gland which regained normal size in three months. On the basis of this finding and the experimental results of Hughes, he suggests that thiouracil should be replaced by iodine some weeks before delivery.

Toxicity.—Toxic manifestations, which are said to occur in 10 per cent of cases (Williams), may be divided into two groups, (1) those due to overdosage and (2) those due to idiosyncrasy of the patient (Himsworth). When too much of the drug is being given the subject may feel weary and depressed and have a bloated appearance resembling hypothyroidism while the blood cholesterol may begin to increase. The thyroid gland becomes larger and may even produce pressure symptoms. Idiosyncrasy to the drug is said to be due to increasing sensitivity and not to cumulation. Himsworth reports on a fairly severe reaction after one dose of the drug. The manifestations are varied and include fever, skin rashes, lymphadenopathy, enlargement of the submandibular glands, pharyngitis, diarrhoea, regional oedema, arthralgia, renal involvement, jaundice (Sloan and Shorr), heart block, pericarditis (Bain) and, most important of all, changes in the blood. The complication which is especially to be feared is a reduction in the granular leucocytes of the blood accompanied in a few cases by a reduction in the number of platelets and by purpuric haemorrhages (Dunlop). Often this leucopenia is transient, but it is very difficult to be certain that it will be so since, according to Himsworth, the production of agranulocytosis is unpredictable except that it will occur during the first two weeks of treatment if it is going to occur at all. It is advisable therefore to watch the total leucocyte and differential counts particularly during the early stages of treatment since only by making repeated blood examinations is it possible to avert a catastrophe. Experimental work on the rat indicates that there is a factor in liver which prevents the diminution of granulocytes during the administration of thiourea and it seems advantageous to give liver to patients on thiouracil treatment (Goldsmith and his colleagues).

Pre-operative use.—It is still too early to decide the exact place of thiouracil in the pre-operative treatment of thyroidectomy. Reports are available from various surgical departments and on the whole they seem to be favourable to its use. Moore and his colleagues report on a series of thirty-four patients who were given thiouracil prior to operation. The clinical response was satisfactory, and the fall in the basal metabolic

rate was more marked and more rapid than was the case with iodine therapy. The thyroid gland in nearly every case became more vascular, leading frequently to the appearance of a bruit and thrill over the gland. There is no doubt that the increasing hyperplasia, vascularity and friability of thyroid tissue renders the actual operation more troublesome because of the more difficult control of haemorrhage, especially if the patient has had a previous thyroidectomy. Postoperatively, however, Moore and his co-workers as a rule found that the course was smoother than it was after iodine administration but was distinctly more disturbed than after the removal of a simple goitre. This indicates that thiouracil, in spite of the normal basal metabolic rate, has not established physiological equilibrium.

Oestrogens

Evidence is accumulating that stilboestrol has a place in the treatment of prostatic cancer. It is still uncertain whether either castration or continued administration of stilboestrol leads to permanent arrest of the cancerous growth, but there is no doubt that either form of treatment is of considerable value in the temporary alleviation of the disease. In both the underlying principle is the same, namely reduction in the supply of male hormone. Castration removes the source of supply whereas stilboestrol inhibits the production of gonadotrophin by the anterior lobe of the hypophysis which is the necessary stimulus for the production of the androgen. Dean, Woodard and Twombly compared the results of the two methods of treatment and found that castration acted more rapidly but that relapses were less frequent when stilboestrol was administered, and this is now preferred by the authors. Stilboestrol is given in doses of 1 milligram three times weekly, increased if necessary to 5 or even 10 milligrams every day. Relief from pain, lessened frequency of micturition, improvement in appetite, increase in weight and rise in the haemoglobin concentration occurred fairly quickly in nearly all the patients (Nesbit, Pazzos and Cummings). Watkinson and her collaborators found that the serum acid phosphatase fell rapidly to within normal limits and maintained this level for considerable periods. Peck has reviewed a series of 300 cases of prostatic carcinoma in which the patients were treated by castration or with administration of stilboestrol or other oestrogen, relief from pain occurred in some subjects within twenty-four hours. There was a gross parallelism in the fall of serum acid phosphatase and clinical improvement, and it would appear that an increase of acid phosphatase indicates the rapid growth of metastases.

Binnie has reported on cases which suggest that stilboestrol may be of help in the treatment of mammary cancer and its metastases. Haddow, Walkinson and Paterson have investigated the effect of other synthetic oestrogens including triphenylchlor-ethylene and triphenylmethylethylene. In breast cancer there was temporary retardation of the growth in ten of the twenty-two cases, the highly cellular carcinomata being more sensitive than were the scirrhous varieties. In advanced malignant disease of other regions no effect was noted on the course of the disease.

It is well known that lactation is maintained by one of the hormones of the anterior lobe of the hypophysis, the release of which is prevented by oestrogens. It seems logical therefore to use the latter hormones for the inhibition or suppression of lactation. Walsh and Stromme, using stilboestrol, were completely or partially successful in inhibiting or reducing lactation in more than half the number of their cases. The drug was particularly effective in preventing or minimizing the intensity of breast pain and in greatly reducing the incidence and degree of breast engorgement. The results were not so satisfactory in patients in whom lactation had already commenced before the institution of hormone therapy. There were some unpleasant manifestations associated with the treatment, such as gastro-intestinal upset, erythema, angioneurotic symptoms and even exfoliative dermatitis. The recommended dosage is 10 milligrams, followed by two further doses of 5 milligrams at intervals of twenty-four hours, all doses should be given orally. O. H. Bloom claims better results when stilboestrol (diethylstilboestrol) is combined with dimethylstilboestrol, which acts more slowly but for a longer period. Prescott and Basden found that the best results were obtained when still another synthetic oestrogen, hexoestrol dipropionate in oil, is given by intramuscular injection with this method no unpleasant side-effects were noted.

Among other uses recorded for the oestrogens may be mentioned their employment in the treatment of primary or major secondary vasomotor disturbances. McGrath and Herrmann obtained promising results in 345 patients of both sexes, of ages

ranging from 14 to 83 years, by the use of α -oestradiol dipropionate in doses of 0.5–1 milligram three times weekly for a period of eight weeks.

It is not necessary in this review to state that at present there is a notable indication for stilboestrol and its allies in the treatment of vasomotor disturbances of the menopause, but it may be of help to emphasize that they have certain disadvantages. Novak has stressed the importance of postmenopausal metrorrhagia and its significance. He mentions four simple precautions, as follows: (1) avoidance of the use of oestrogens unless the symptoms are clearly menopausal and really constitute a problem to the patient, (2) avoidance of so-called prophylactic oestrogenic therapy, (3) avoidance of unnecessarily large doses and (4) avoidance of routine fixed dosage for prolonged periods and use of the drug only if and when it is needed.

Morphine

Comparative studies made on a group of twenty-four healthy subjects showed that a given dose of monoacetylmorphine is about four times as effective as is a similar dose of morphine sulphate in the control of cutaneous pain (produced by the heat radiation method); unpleasant side-reactions, especially nausea and vomiting, are less commonly encountered with the newer drug (Jones and Chapman). An experimental study by Woolfe and Macdonald indicates that morphine is about seven times as active as is codeine and is half as active as diacetylmorphine (diamorphine) whereas pethidine is ineffective against severe pain. Beecher points out the risks involved in giving repeated subcutaneous injections of morphine to patients with sluggish circulation: the morphine fails to relieve pain because it is not absorbed until the circulation is re-established, when all the injected drug may be absorbed so rapidly that signs of poisoning become manifest. Beecher states that the intravenous use of morphine would eliminate this risk, but if this is not practicable the drug should be given intramuscularly and the site should be massaged. Peterson, Bornstein and Jasper publish the results of experiments on the effect of morphine sulphate at high altitude barometric pressures, a matter of importance in the transport of the sick and wounded by air. When the reflex excitability of the central nervous system is at a reasonably high level, a $\frac{1}{4}$ grain of the drug does not alter the average blood oxygen saturation or reduce the ability to respond to oxygen administration. When, however, reflex excitability is not maintained after the administration of morphine there is a deterioration in blood oxygen saturation but no reduction in the ability to respond to oxygen administration.

Antacids

The search for the ideal antacid continues. The basic aluminium salt of aminoacetic acid has been prepared with the double purpose of (1) effecting immediate neutralization of acid by the amino group and (2) securing a prolonged buffering of the hydrochloric acid by interaction with the aluminium salt. The salt, which mixes easily with water to form a bland stable suspension, is more efficient than is the dried aluminium hydroxide gel and has been found to be useful in the treatment of hyperacidity and peptic ulcer (Krantz, Kibler and Bell). A 4 per cent solution of aluminium phosphate gel given in a dose of 30 cubic centimetres three times daily after meals, at bedtime and when there is pain during the night, yielded good results with fairly rapid improvement, as shown by x-ray examination, in peptic ulcer. In some cases intranasal gastric drip of a 1–3 dilution of the gel was given at the rate of 15 drops per minute throughout the twenty-four hours (Lichstein, Simkins and Bernstein). Sodium alkyl sulphate—a combination of sodium lauryl sulphate, sodium palmityl sulphate, sodium stearyl sulphate and sodium oleyl sulphate—which has been found to have a marked inhibitor effect on pepsin, was used in doses of 0.2 gramme every two hours throughout the day, and appeared to promote healing of some ulcers that were resistant to other forms of therapy (Fogelson and Shoch). It should not be forgotten that with these and other methods of ulcer treatment it is very difficult—if not impossible—to evaluate results with accuracy.

In this connexion the experimental and clinical findings of Roth, Ivy and Atkinson on the effect of caffeine on the stomach are worth mention. In large doses this drug causes acute and subacute gastric ulceration in cats; moderate doses increase the gastric secretion, acting synergistically with histamine or alcohol. Coffee and coffee substitutes prepared from roasted cereals stimulate the secretion of gastric juice and in patients with peptic ulcer provoke a prolonged increase in the total output of acid. For these reasons these workers believe that the excessive use of beverages containing

caffeine may contribute to the pathogenesis of peptic ulcer in the susceptible individual and may render the therapeutic management of the case more difficult

Sympatheticomimetic drugs

Dodd and Prescott, as a result of controlled observations on fifty-four patients, come to the conclusion that Methedrine (desoxyephedrine) is an effective pressor agent with a gradual prolonged action and without undesirable effects, given in doses of 15–30 milligrams intramuscularly or 10–15 milligrams intravenously plus a depot dosage of 10–20 milligrams administered intramuscularly. A rise of blood pressure occurs within a minute of intravenous injection and reaches its maximum in from two to ten minutes, after intramuscular administration the rise commences in from two to ten minutes, reaches its peak in from four to thirty eight minutes and is prolonged even up to forty-eight hours. Pulse pressure is increased and there is an increased rate and depth of respiration. Like amphetamine, Methedrine acts as a cortical stimulant, producing euphoria, and is capable of abolishing the effect of morphine ($\frac{1}{8}$ grain) and scopolamine (hyoscine) ($\frac{1}{16}$ grain). Only in doses exceeding 60 milligrams does it produce palpitation, restlessness and other unpleasant symptoms. Prescott compared its clinical effectiveness with that of Paredrine, Neosynephrine and pholedrine and, on the basis of rise of systolic and pulse pressures in patients with a systolic pressure of 80 millimetres or less, of speed and duration of action and of relative freedom from side effects on the cardiovascular system, concluded that Methedrine gave the best results.

Ethyl-norsuprarenin [1 (3, 4 dihydroxyphenyl)-2 amino-1-butanol hydrochloride] on the other hand is a sympatheticomimetic drug which does not raise the systolic blood pressure although it increases pulse pressure and pulse rate and therefore the volume flow of the blood without a proportional increase in the work of the heart. It is effective in the relief of asthma and has fewer and less marked subjective side-effects than has adrenaline (Tainter and his colleagues).

Amphetamine and *d*-desoxyephedrine have been reported to be of value in combating the weakness, exhaustion and lassitude of irradiation sickness (Jenkinson and Brown). Kully has discussed the use and abuse of nasal vasoconstrictor medication. The primary vasoconstricting effect of the sympatheticomimetic drugs is usually followed by secondary vasodilatation which is influenced by the type and amount of drug employed and the sensitivity of the individual patient. The addition of antiseptics, especially sulphathiazole, to the vasoconstrictor increases the irritant effect without therapeutic benefit. Although judicious use of vasoconstrictors is indicated in surgical procedures and in some acute nasal infections, especially acute sinusitis, in acute rhinitis it may lengthen the course of infection and increase the incidence of complications. Furthermore, vasoconstrictor drugs may themselves produce a vasomotor rhinitis. It is clear therefore that they should be used sparingly and certainly for not more than a few days at a time.

mercurial diuretics. Wexler and Ellis report on two fatal cases and Rennie on a third. These deaths occurred within a minute or two of an intravenous administration after a series of injections had already been given. Pines, Sanabria and Arriens consider that the fatal reaction is due to a direct effect of the mercury on the heart, producing disturbances of the conduction system and ventricular fibrillation. They state that the addition of 0.5 cubic centimetre of 20 per cent magnesium sulphate to a lethal dose of a mercurial diuretic prevents ventricular fibrillation and the death of experimental animals. Non-fatal reactions vary in severity, being divided into those which are immediate and those which are delayed. The immediate reactions are probably due to an action on the myocardium whereas the delayed are attributable to the diuresis. After the intravenous injection of a mercurial diuretic there is a fall in plasma volume as well as a reduction in venous pressure and pulse pressure with symptoms suggesting a decrease in cardiac output (Lyons, Avery and Jacobson). Wexler and Ellis recommend intramuscular injections and Batterman, DeGraff and McCormack have obtained satisfactory results from the oral use of Mercupurin (mercurophylline), two tablets three times daily for two or three days. Ammonium chloride appears to enhance the diuretic effect. If repetition is necessary, the mercurial tablets should be given in courses from three to five days apart.

Salicylates

Of great interest is an important paper by Coburn¹ on salicylate therapy in rheumatic fever. Briefly, Coburn's hypothesis is that the serum salicylate must be maintained at a level of at least 350 micrograms per cubic centimetre if the rheumatic reaction is to be held in check. This can be achieved only by intravenous administration: 10 grammes of sodium salicylate in 1,000 cubic centimetres of 0.9 per cent sodium chloride are injected by intravenous drip over a period of from four to six hours every day for four days. His case reports show rapid resolution of the acute phase of the disease as judged by the sudden disappearance of clinical signs and the rapid fall of the blood sedimentation rate. It is still much too early to state whether this new method of treatment will actually cure the disease and prevent recurrences—its use is clearly limited to hospitals which have an efficient follow-up department.

The use of large doses of salicylates is not without risk and should not be allowed without careful clinical observation of the patient. The minor side-reactions and the much more serious salicylate acidosis have long been known. Recently it has been shown that compounds of salicylic acid lead to a decrease of the prothrombin content of the blood (Meyer and Howard). This may be sufficiently serious to produce haemorrhages. Ashworth and McKemie have reported two deaths with widespread hyperaemia and haemorrhages, particularly involving the brain. Shapiro has found that approximately 1 milligram of synthetic vitamin K counteracts the prothrombinopenia-inducing effect of 1 gramme of acetylsalicylic acid. He suggests that whenever salicylates are given in large doses or over long periods the prothrombin time should be estimated and vitamin K should be given as required. Charters and Hopkins each report the clinical findings in a case of aspirin poisoning. It would appear from the Registrar-General's figures that for the period 1938–1942 aspirin poisoning is the cause of some fifty deaths annually. N. Bloom and Walker record the onset of a condition resembling anaphylactic shock with transient nodal rhythm and bundle-branch block after the ingestion of 5 grains of aspirin. "The mass of evidence so far available indicates that aspirin and the salicylates are among the least toxic of active pharmacopoeial preparations. This status, however, should not be interpreted as an excuse for failure to recognize hazards connected with their abuse or even under certain circumstances of established usage" (Editorial).

Dicoumarin

This substance reduces prothrombin activity and therefore slows down coagulation. Its use appears to be indicated whenever there is any tendency to intravascular thrombus formation. It is effective when given orally. A daily dose of 300 milligrams for two days followed by 50 milligrams per day led to a marked increase in clotting time within three days without any alteration of bleeding time (Geftter, Kramer and Reinhold). The use of the drug is not, however, without risk since the margin of safety is not wide. Crawford and Nassim report on a case which illustrates the variability of response. The drug may remain active for nearly a fortnight after administration

ceases, and in their case gross haematuria lasted for nine days. Repeated estimations of prothrombin activity are essential if dicoumarin is to be used as a therapeutic measure. Whenever there is a tendency to haemorrhage, renal insufficiency or liver impairment associated with vitamin K deficiency the use of dicoumarin is contra-indicated. It has, however, proved to be of value if used with care in the prevention of postoperative thrombosis, and in limiting the extension of thrombi already formed, as in the puerperium (Davis and Porter). Sulphonamide therapy is no contra-indication to its use, provided the functions of kidneys and liver are within normal limits (Brambel and Loker).

Heparin reduces coagulability much more rapidly but its effect is very transient and it must be given intravenously. When a rapid and prolonged effect is desired heparin should be used to reduce coagulability for about thirty-six hours, that is, until the dicoumarin activity has become apparent.

Potassium thiocyanate

Interest is still being maintained in the use of potassium thiocyanate for reducing blood pressure. Some of the reports are encouraging (Blumenthal and Wetherby, D'Silva and Evans, Kofler, Freireich and Silverman) but it is clear that this remedy must be used only when there are facilities for making repeated determinations of the thiocyanate level in the blood, which should not exceed 12 milligrams per cent. The usual dose employed is 3 grains daily, to be increased by 3 grains every week if a satisfactory fall of blood pressure is not achieved and the blood level does not reach the critical value. In all cases the blood level should be kept as low as possible compatible with the wellbeing of the patient and the lowering of the blood pressure. Symptomatic relief was in every series a more marked feature than was any effect on the blood pressure. Rawson, Hertz and Means report on the development of goitre in two patients who received the drug for hypertension. This can be relieved by the administration of thyroid even when thiocyanate treatment is continued. In general, however, toxic effects were neither common nor serious when attention was paid to the concentration of the drug in the blood.

Proteins and amino-acids

Recent work has shown that in both acute and chronic disease lack of protein and particularly of one or more amino acids may play a decisive part by interfering with recovery. It is out of place here to enumerate the various conditions in which hypoproteinaemia occurs, but to indicate its importance in clinical work it is worth mentioning that hypoproteinaemia is found in cardiac oedema, liver disease, extensive burns and coeliac disease and in some forms of kidney disease. There are various methods of replenishing the diminished stores of protein. Oral administration is clearly the method of choice, and when assimilation is effective and liver function unimpaired a high protein diet is indicated. Recently it has been suggested that methionine, a sulphur-containing amino-acid, is of particular importance in maintaining nitrogen balance (Croft and Peters). Of particular interest is the effect of this substance in protecting the liver. Experimentally in rats Himsworth and Glynn demonstrated this protective action on the liver and Goodell, Hanson and Hawkins showed that arsphenoxide hepatitis in dogs kept on a protein-deficient diet was prevented by administration of methionine. The evidence in man is not so conclusive. The results obtained by Beattie and Marshall and by Beattie and other colleagues in post-arsphenamine jaundice and in infective hepatitis lead these workers to suggest that methionine has a beneficial value in these conditions. R. A. Peters and his co-workers also state that cysteine and methionine have an effect on arsenical jaundice which although not striking is quite significant. Other workers, however, have not been impressed. Turner and his colleagues failed to demonstrate any effect in over 4,000 cases of homologous serum jaundice, and C. Wilson, Pollock and Harris observed no significant effect, either as regards the severity or the duration of the disease, in 100 patients with infective hepatitis. Higgins and his colleagues drew a parallel between eighteen patients treated with a low fat, high-protein diet and a comparable group of eighteen on the same diet plus 5 grammes of methionine. No difference was noted in the clinical course, symptomatology or biochemical findings. There seems to be little doubt that protein in sufficient amount is necessary for the efficient functioning of the liver cells. There is some experimental evidence to indicate that extra protein, with a

large content of sulphur-containing amino-acids such as methionine and cysteine, is of value in protecting the liver from some chemical or biological poison. It must, however, still remain an open question whether these amino-acids play a significant part in re-establishing normal functioning once the poison has already affected the liver cells. The good result obtained by Beattie and his colleagues with the immediate administration of methionine after a large dose of a potent liver poison (carbon tetrachloride) suggests that this amino-acid may be of value when it is supplied very soon after the onset of hepatic involvement. There is some evidence that methionine may be of particular value in the treatment of skin diseases such as exfoliative dermatitis (B. A. Peters) and in the treatment of burns (Croft and Peters).

Since 1939 attempts have been made to use protein hydrolysate intravenously. A review of the literature up to 1943 has been made by Gaunt. During the past year reports have been available of the successful use of intravenous administration of casein hydrolysate in the treatment of severe starvation (Krishnan, Narayanan and Sankaran) and of idiopathic steatorrhoea (Emerson and Beckman). Magnusson has had good results in the case of premature infants with the oral administration of a casein hydrolysate mixture containing 25 per cent amino-acids, 25 per cent glucose and 1.5 per cent salts, given in daily doses of 10 cubic centimetres per kilogram of body weight.

Perhaps the most important advance in the therapeutic use of proteins has been heralded by the successful fractionation of the plasma proteins by Cohn alone and with his colleagues. Five fractions are described of which the most important are albumin and γ -globulin. Albumin is of especial importance in the maintenance of the osmotic pressure of the plasma. It can now be prepared as a 25 per cent solution with the same viscosity but four times the osmotic activity of whole plasma: such a solution containing merthiolate or other antiseptic as preservative has a high degree of stability and is valuable in conditions in which there is hypoproteinaemia, especially when there is a demand for prompt restoration of the blood volume (Janeway). γ -globulin, which forms about one-tenth of the plasma proteins, contains almost all the antibodies of the blood. The latest preparation of this protein represents a 25-fold concentration of the antibodies in the original plasma and can be heated sufficiently to destroy the virus of infective hepatitis without altering the potency of the immune bodies. It cannot be given intravenously but intramuscular injections are safe. It seems to be likely that it may replace convalescent serum and placental extract in the prevention and treatment of measles. Greenberg, Frant and Rutstein have compared γ -globulin with placental extract and have shown that the former was more effective in the younger age groups. If it is prepared from plasma obtained from a sufficiently large number of donors it is likely to contain antibodies to the toxins of whooping cough, chickenpox, mumps and poliomyelitis (Leading Article ⁴). Of the other proteins, thrombin, contained in a matrix of fibrin, has been used as a haemostatic in neurosurgery and in controlling bleeding from oozing surfaces and in haemophilia. Fibrinogen has been utilized to prepare plastic-like fibrin films which have been found to be of value as dural substitutes and in the prevention of meningocerebral adhesions (Leading Article ³).

Vitamins

Because of the widespread phobia of vitamin starvation it is worth while mentioning the findings of Bransby and his collaborators that supplements of vitamins A and D, thiamine, riboflavine, nicotinamide and ascorbic acid had no statistically significant effect on the rate of growth, the nutritional status, the muscular strength, the state of the teeth and gums or the incidence of illness of schoolchildren, or on the health, weight, haemoglobin or blood pressure of adults, during the period between November 1941 and August 1942. Similar results were obtained by Ruffin and Cayer in the United States. In Edinburgh schoolchildren, Davidson and Donaldson found that a daily supplement of 25 milligrams of ascorbic acid did not have any effect in raising the haemoglobin levels, and the incidence of bleeding gums in the personnel of Royal Air Force stations was not reduced by the administration of this vitamin (Stamm, Macrae and Yudkin).

An excellent article on vitamin dosage has been written by Asher; this gives details of the vitamin contents of the various pharmaceutical and other preparations available.

The vitamin B complex has been given with liver extract parenterally to patients with

coeliac disease. In all, satisfactory gains in weight and in height were observed with improvement of general health in the early weeks of treatment. Diminution in stool fats occurred in all but four cases, the oral blood sugar curves returned to within normal limits but the vitamin A absorption curves still remained abnormal (Paterson, Pierce and Peck)

Bourne has shown that in vitamin C-deficient animals fibroblastic activity in aseptic wounds is diminished and retarded. Meyer and Meyer found that in septic wounds phagocytic activity and fibroblastic growth were at a much lower level when the experimental animals were scorbutic. They conclude that vitamin C is important in combating infection in which rapid production of fibrous tissue is an integral part of the body's defence.

Because of the irregular administration and inadequate dosage of vitamin D preparations when given by mothers in their own homes, Krestin investigated the value of single massive doses of vitamin D in the prophylaxis of rickets. He found that one dose of 300,000 international units (7.5 milligrams of calciferol), given orally, protected 40 out of 43 infants under the age of one year and that there were no ill effects. This method of prophylaxis may be worth considering for the infants of negligent mothers of a low grade of intelligence.

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ABORTION

See also B.E.M.P., Vol. I, p. 47; and Cumulative Supplement, Key No. 12.

Natural and unintentional abortion

Causes

Part played by vitamin deficiency.—King reviews the aetiology of abortion, presents his findings in a study of prothrombin time and vitamin C levels in cases of abortion, comparing them with those of other series, summarizes recommended therapy and evaluates its results. The literature indicates that pathological fetal or maternal elements probably account for a large percentage of abortions, therefore, before undertaking parenthood, both partners should be in the best possible health. King's study is based on 82 patients who had aborted or who would inevitably abort, 18 patients with threatened abortion, and 35 unselected healthy individuals. Of the abortion series, 52 per cent had prothrombin values of 70 per cent or less, 21 per cent had vitamin C levels of 0.5 milligram or less. Of the control group, 24 per cent had deficient prothrombin time levels and 13 per cent had vitamin C deficiency, these levels being not appreciably different from those found in the threatened abortion group. Eight of the latter aborted, but only one had a low prothrombin level and none was vitamin C deficient. Further studies are required to determine both the effectiveness of vitamin E in threatened abortion and the optimum dosage, since, given as Eprolin in large amounts in King's series, it proved to be ineffective. Proklot, a synthetic vitamin K preparation, has shown itself to be effective, without additional bile salts, if given after meals to persons with normal biliary function. Morphine, being oxytocic, is contra-indicated. Small or moderate doses of progesterone are preferable to large ones which may destroy the intrinsic supply. In summary, the elective treatment of threatened abortion would appear to be complete rest in bed, full nutritional diet with additional vitamins C and K, if deficiencies of these have been found, sedation with barbiturates and either oral or parenteral administration of corpus luteum hormone.

Artificial and intentional abortion

Medical grounds for abortion

Controversial factors.—Opening with some ironical allusions to medical "ethics" and later quoting Greenhill as saying, "We consider the operation of induced abortion one of the most dangerous in obstetrics", Cosgrove and Carter discuss the controversial social and medico-legal problem of therapeutic abortion. As a direct result of this procedure 5.5 per cent of patients in a first-class American clinic died. The authors accept a definition of abortion as "the termination of a previable uterine pregnancy; i.e., the expulsion or extraction of a live or a stillborn fetus before the seventh month (twenty-eighth week) of gestation". They quote the differing laws which obtain in the American States and mention the curious fact that "very few jurisdictions require that the determination of the necessity of abortion to save the mother's life must depend on medical men, or that the procedure when so determined, be carried out by medical men". Cosgrove and Carter list the commonest indications for therapeutic abortion as follows. (1) Hyperemesis gravidarum; this they consider to be almost always curable without abortion when modern hospital and therapeutic resources are available; (2) toxæmia of pregnancy; this they do not think is often an indication; (3) fixed hypertension—in the severer cases of which the patients often abort spontaneously—the authors consider to present difficult and urgent problems although it is emphasized that approximately one-third of the number of even severe cases are not prejudiced by pregnancy in their subsequent condition and course; (4) heart disease; here actual cardiac failure only is considered to be a justification of abortion; (5) pulmonary tuberculosis; the influence of this disease on pregnancy the authors regard as a bitterly controversial subject. Cosgrove and Carter emphasize that socio-economic factors and problems inevitably bear upon the whole thorny question of abortion, therapeutic or criminal. In the course of a discussion arising out of this paper, Rosensohn mentioned an interesting Californian legal decision that immediately after the moment of conception a child becomes entitled to inherit, a physiological view which is quite opposed to the principle of English Common Law but supports the authors' contention that abortion, albeit sometimes justifiable, is always "murder".

Illegal abortion

Fatal use of an abortifacient paste.—Straus and De Nosaquo report details of a death due to an abortifacient paste, together with its effects and those of each component ingredient experimentally given to pregnant rats and rabbits. The patient, 22 years of age and pregnant for 6 weeks, was made to abort by the introduction into the uterus, twice with a 2-day interval, of a paste composed of castor oil-potassium hydroxide soap, pine oil, alkali-combined iodine and water. The patient began to bleed from the uterus 24 hours after the second injection and was admitted to hospital on the fifth day with signs of acute peritonitis. She died 56 days afterwards. The endometrium was greenish grey, the myometrium was

oedematous and there was a perforation near the right horn of the fundus. Sections near the perforation revealed extensive inflammation. In the myometrium were masses of orange coloured granular material. The effect of the paste on human blood is similar in appearance to the vacuolated masses seen in uterus and ovary. The paste caused perforation of the uterus of a pregnant rabbit which died after a week. Abortion was caused in 2 pregnant white rats, with suppurative inflammation of the uterine wall. The ingredients separately applied failed to cause similar masses in the myometrium.

Severe vaginal bleeding caused by potassium permanganate—McDonough reports on 65 cases of vaginal bleeding due to the use of potassium permanganate as an abortifacient. None of the patients, whose ages varied from 18 to 38 years, gave an accurate history. On being specifically questioned, 22 patients admitted using potassium permanganate, but, until after detection of the lesion 43 denied having used any method of inducing abortion. Onset of profuse bright red bleeding usually occurred less than 2 hours after insertion of the tablet. Fresh bleeding persisting after removal of vaginal clots and a palpable irregularity on the neck of the uterus or the vaginal mucous coat usually indicated the diagnosis. Speculum examination as a rule showed there to be one or more eroded areas covered by a black eschar, often situated in the posterior fornix on the mucosa of both the neck of the uterus and the vagina. Rigid treatment for shock was required in 12 cases, vaginal packing for 48 hours in 34 cases, and suturing of bleeding points in 10 cases. Only 6 patients succeeded in producing abortion. There were neither deaths nor evidence of generalized toxic symptoms, but serious sequelae occurred in one woman, who required insertion of 3 mattress sutures into a large bleeding crater on the posterior lip of the neck of the uterus, extending into the posterior fornix of the vagina. Subsequent cicatricial distortion of the neck and fibrous replacement of the posterior fornix necessitated Caesarean section at term. McDonough emphasizes the importance of including the condition described in the differential diagnosis of all cases of vaginal bleeding occurring during the childbearing age, and stresses the dangers of improper treatment based on an incorrect diagnosis of threatened abortion.

Cosgrove S A, and Carter, Patricia A (1944) *Amer J Obstet Gynec*, 48, 299

King, W E (1945) *Surg Gynec Obstet*, 80, 139

McDonough J F (1945) *New Engl J Med*, 232, 189

Straus, R. and De Nosaquo, N (1945) *Arch Path*, 39, 91

ACCESSORY SINUSES OF THE NOSE

See also B E M P Vol I p 77, and Cumulative Supplement, Key Nos 15-17

The accessory sinuses of the nose

Inflammatory diseases

Radiography of the paranasal sinuses—Hallberg remarks that radiography now plays a considerable part in the diagnosis of diseases of the paranasal sinuses. Its use is indicated in the following cases: (1) when unequivocal clinical evidence of sinusitis such as an external fistula is present, (2) when a history of recurrent attacks raises the suspicion of chronic infection, (3) when the patient asserts that he has sinusitis, (4) when pathological findings such as pus, changes in the mucous membrane, nasal allergies and polypi are disclosed by routine examination of the nose, (5) when patients have some pulmonary condition e.g. chronic bronchitis, asthma or bronchiectasis, which is often associated with sinusitis, (6) for the purpose of enabling the exact anatomical condition to be ascertained before any operation on the sinuses is undertaken, (7) when a growth of one of the sinuses is suspected alone. In all cases the radiological findings must be correlated with those of clinical examination if they are to yield their most valuable results. Radiography alone cannot distinguish between active and healed or quiescent disease. If symptoms are not present, thickening of the mucous membrane of any of the sinuses discovered on routine x ray examination is without significance.

Acute sinusitis

Treatment by penicillin—Hauser and Work describe the results of the treatment of sinusitis with penicillin. They first used the drug with rapid and dramatic success on 2 patients: (1) an airman with suppurative sinusitis following an air crash injury, (2) a soldier with a localized osteomyelitis of the frontal bone after a 2-month history of frontal sinusitis. Similar successes were obtained in 4 further cases of sinusitis. The authors, thus encouraged, decided to use the drug more extensively in treating various types of sinusitis and they report on a series of 28 cases classified into 5 groups. In 3 cases of allergic rhinitis with superimposed infection treatment with 15 000 units of penicillin, given intramuscularly, eliminated all signs of infection but the authors consider it improbable owing to the underlying pathological state that a permanent cure resulted. In 4 cases of orbital sinusitis the intramuscular injection of penicillin resulted in a rapid and dramatic cure. The last 3 groups classified are: (1) 3 cases of suppurative rhinosinusitis, secondary to shrapnel wounds, the treatment of which included surgery, (2) 9 cases of suppurative sinusitis in which surgical treatment involved the maxillary sinuses only, (3) 9 cases in which a radical operation was performed on the frontal and ethmoid sinuses. Hauser and Work state that in those cases in which penicillin was used with adequate surgical treatment the results attained were better than those they obtained previously without using penicillin. They say that their method of choice for the administration of penicillin is 20 000 units given intramuscularly at 3 hour intervals.

In their most recent cases they have been giving penicillin 48 hours pre-operatively. They conclude that penicillin is a most important adjunct in the treatment of sinusitis. In orbital cellulitis the authors use it in preference to any other method of treatment. It appears that chronic suppuration sinusitis, of relatively short duration only, can be cured by penicillin therapy alone; but in long-standing cases the drug used by itself seems to have little, if any, value, although when its use is combined with adequate surgery a rapid and complete cure results.

Chronic suppuration

Treatment by decompression.—Butler, Greenwood and Ivy describe the results of decompression treatment of 125 patients with subacute and chronic sinusitis. All had had sinusitis for several years (average $9\frac{1}{2}$ years), with distinct symptoms, and had undergone various treatments—operation, lavage of sinuses after cannulation or puncture, displacement therapy, siphonage, vaccine injections, diathermy and nasal packs. No cases of active sinusitis were included. Treatments were given in a high altitude chamber, and consisted of rapid decompression to the pressure of an altitude of 10,000 feet, at the rate of 5,000 feet per minute, and slower recompression to the pressure at 5,000–6,000 feet, at the rate of 700 feet per minute. This procedure was repeated 4–6 times, when slow descent to ground level completed the treatment. Eighty-nine per cent of patients were relieved of symptoms, some after only one or two treatments, but the average number of treatments necessary per patient was 18.1. Permanence of results was very variable, some patients showing no return of symptoms in a period of over 2 years; in others symptoms returned with acute infections of the upper respiratory tract, and in a larger number regular treatment was necessary in order to prevent recurrence. Headache and nasal congestion and pressure were consistently relieved, and deafness was improved in 33.3 per cent of the 9 patients showing this symptom. In no case were the symptoms aggravated or increased. Aero-otitis media occurred only 10 times in 1,472 treatments, a remarkably low rate of incidence considering that all the patients had infections of the upper respiratory tract. In all 10, except one which was over-energetically treated, the condition subsided without sequelae. Thirty out of 42 patients who had repeated rhinological examinations showed sinus improvement after decompression, and x-ray examinations in others also showed improvement. Whether or not decompression can “cure” is not yet settled but it undoubtedly can give relief to the chronic sufferer.

Sinusitis in children

Essentials of treatment.—McMahon, in discussing the treatment of sinusitis in children, states that it is liable to occur when there are unhealthy environmental or nutritional factors present. The ethmoidal and maxillary sinuses are those most frequently affected. Inflammation of the nasal and sinus mucosa is greater in a child than in an adult since the epithelium is more vulnerable to trauma and bacterial attack, although the clinical pathology is the same. Undernourished children suffering from frequent “colds”, enlarged tonsils and adenoids or a deviated septum are most liable to get sinusitis. Symptoms consist of unilateral or bilateral congestion of the inferior and middle conchae with nasal discharge, pyrexia, headache and malaise. Spread to the meninges or the orbital cavities may occur or general systemic infections such as bronchitis or pyelitis may ensue. Investigation of the child's general condition should always be undertaken in order to eliminate any allergic factor or nutritional cause and adequate vitamin therapy should be given. Local treatment should conform as far as is possible to that given to an adult, although this depends to a great extent on obtaining the child's cooperation. Nasal irrigation is necessary when the nasal cavities are blocked with pus; the author advocates the use of physiological saline, followed by the instillation of ephedrine hydrochloride 1.5 per cent in physiological saline or Neosynephrin hydrochloride (1- α -hydroxy- β -methylamino-3-hydroxy-ethylbenzene hydrochloride) $\frac{1}{2}$ per cent when there is a reaction to ephedrine. It has been stated that 80 per cent of cases are cured by adequate removal of tonsils and adenoids. Polypi should be removed and it may be necessary to resort to antral puncture if the condition becomes chronic. More extensive sinus surgery in children is justified only in extreme emergencies. Finally, the systemic use of sulphonamides and penicillin appears to be of value in the treatment of sinusitis.

The chronic running nose in children.—Treatment of the chronic running nose in children depends largely upon an appreciation of the anatomy and physiology of the nose and its accessory sinuses. The main points are enumerated by Wells. The area of mucous membrane lining the nasal passages is about 40 square inches and there is lymphatic continuity between the nose and sinuses, lymphatic glands around the larynx and lymphatic vessels of the orbit, cranial cavity and posterior parts of the neck. Disturbances in the nose may therefore produce distant effects. All nasal discharge results from inflammation and treatment should be aimed at promoting the reaction of inflammation so that organisms, toxins and broken-down tissue cells may be removed as speedily as possible. Measures directed to this end include irrigation, radiant heat, suction, ultra-violet rays, diathermy, solutions of drops and sprays, zinc ionization and diastolization. Most cases of sinus trouble in children can be relieved successfully by suction as in the Proetz displacement method. Treatment of tonsils by tonsil suction should be more extensively used and no tonsils should be removed before any coexisting sinus condition has been treated. General treatment is of great importance and involves housing, ventilation and school hygiene. All victims of catarrh should reduce the

intake of sugars and starches and should have garden produce daily in their diet Wells maintains that every child who leaves a fever hospital should be kept under observation by the rhinological service of the education authority until the condition of the upper respiratory tract is satisfactory A few minutes at the beginning of every school session should be spent in nasal drill, the nose being first cleaned by blowing through both nostrils and then each in turn Subsequently there should be deep breathing exercises through the nose A vigilant teacher can then refer any child who shows difficulty in carrying out these exercises to the school medical officer and through him to the rhinologist

General

Diagnostic features of individual lesions—Thornell discusses the diagnosis of paranasal sinusitis Fever is common in acute, rare in chronic, sinusitis Pain and associated tenderness—prominent symptoms in acute sinusitis—usually lie immediately over the involved sinus Coughing, straining and stooping aggravate pain Supra-orbital pain, occurring at a certain time daily, characterizes fronto ethmoidal involvement In maxillary sinusitis, pain may extend into the corresponding upper teeth Spheno-ethmoidal involvement may produce deep-seated retro orbital pain or lower facial pain in the distribution of sphenopalatine ganglion neuralgia Headache, unusual in chronic suppurative sinusitis, may occur as pain referred to various facial or frontal areas in chronic hyperplastic sinusitis (infection plus nasal polyp) In chronic sinusitis, nasal or postnasal discharge is usually prominent, but is not diagnostic Partial or complete nasal obstruction may occur in acute and chronic sinusitis Anosmia or foul odour may be produced Anterior rhinoscopy may reveal muco-pus located in the middle meatus of the nose if the drainage is from frontal, anterior ethmoidal or maxillary sinuses, if the drainage is present anteriorly in the middle meatus the material comes from the frontal sinus Pus in the olfactory sulcus and overlying the middle nasal concha suggests infection in the posterior ethmoid cells and sphenoidal sinus After removal of discharge and shrinkage of the nasal mucosa, the head should be placed with the suspected side uppermost for 5 minutes Pus appearing in the middle meatus then suggests maxillary sinusitis Skiagrams reveal the anatomy of the sinuses and the fluid levels present Probing lavage and cannulization are contra indicated in the acute stage, but used later will establish which sinus or sinuses are involved Suction helps in the investigation of the ethmoid cells

Treatment of various types—Williams discusses treatment in five categories of sinusitis In fulminating sinusitis, following sudden production of anaerobic conditions in the frontal sinuses, there may occur necrosis of the sinus mucosa, periphlebitis of anastomosing frontal diploic veins and osteomyelitis Osteomyelitis is commonly due to a micro aerophilic streptococcus, which produces a malignant type of osteomyelitis with a tendency to intracranial extension Treatment is by immediate trephine openings into the sinus floor, lavage with hydrogen peroxide and removal of dead bone present Penicillin destroys the organism but engorgement, sulphonamide therapy is useful and traumatic manipulations are dangerous Local medication with camphor and similar drugs which inhibit the physiological functions of the nasal mucosa should be avoided, as well as sulphonamide solutions which act as cauterants and drugs which produce vasoconstriction with later persistent congestion In acute suppurative and subacute sinusitis, in which the mucosa is less irritable, Williams advocates insertion of a Dowling pack—patches of cotton dipped in 25 per cent solution of mild silver protein—between middle and inferior nasal conchae for half an hour daily After a few treatments the nasal mucosa shrinks, and gentle suction, aided by placing the head in a favourable position encourages drainage through the ostia Lavage through the natural opening, or through an artificial opening if the natural one is occluded, is occasionally necessary in order to remove tenacious mucus In chronic infection of a single sinus, anatomic variations of it or of the nasal septum may hinder drainage, or dental infection may be present Such factors need correction Permanent accessory openings for drainage and aeration should be provided, with maximum conservation of the lining mucosa Pansinusitis associated with bronchiectasis requires surgical cleansing with administration of penicillin in order to prevent postoperative osteomyelitis Uncomplicated pansinusitis needs an adequate intranasal or external operation, depending upon the degree of sclerosis present When infective sinusitis is associated with nasal allergy, surgery must be combined with treatment of the fundamental dysfunction of nasal and sinusal tissues

Butler, D B., Greenwood, G J., and Ivy, A C (1944) *Arch Otolaryng*, Chicago, 40, 266

Hallberg, O E (1944) *Proc Mayo Clin*, 19, 472

Hauser, I J., and Work, W P (1945) *Arch Otolaryng*, Chicago, 41, 161.

McMahon B J (1944) *Ann Otol*, etc., St Louis, 53, 644

Thornell, W C (1944) *Proc Mayo Clin*, 19, 470

Wells, A G (1945) *Practitioner*, 154, 79

Williams, H L (1944) *Proc Mayo Clin*, 19, 474

ACHALASIA

See also B E M P., Vol I, p 116, and Cumulative Supplement, Key No 18

In the alimentary tract

Of the cardiac sphincter

Effects of octyl nitrite—Field describes the effects of octyl nitrite inhalation in 4 cases of

achalasia of the cardia in children. Trial had already been made of amyl nitrite which is effective in relaxing the cardia but on account of its unpleasant disadvantages cannot be persevered with. Glyceryl trinitrate tablets too were tried; these act more slowly and are effective clinically in 1 out of 3 cases. A drug that would be as effective as amyl nitrite and without its disadvantages would be the drug of choice. Octyl nitrite fulfils these requirements and can be administered through an inhaler which contains cellulose pellets impregnated with the drug. The optimum dose is one deep inhalation. The drug was tried on 5 children the fifth child not being benefited by the inhalation because he was found to be suffering from congenital stricture of the oesophagus and not from achalasia of the cardia. The effect of the drug is demonstrated by the swallowing of barium sulphate meals. Generally after $\frac{1}{2}$ –1 minute the cardia relaxes and the barium passes through in from 1 to 5 minutes. Clinically vomiting ceased, discomfort in the chest disappeared, the child became more active and put on weight, although less than would be expected from the improvement in appetite. No toxic symptoms appeared and tolerance of the drug was not established. It is perhaps relevant that in each of the 4 children some upper respiratory infection developed. The children soon discovered the minimal number of inhalations needed to relax the cardia and to empty the oesophagus.

Field, C. Elaine (1944) *Lancet*, 2, 848.

ACNE

See also B.E.M.P., Vol. I, p. 156; and Cumulative Supplement, Key No. 23.

Acne vulgaris

Aetiology

Psychogenic factors.—The importance of the psychosomatic approach to medicine has not escaped the notice of dermatologists. Cohen quotes the observation of Klander that "the influence of the psyche on the skin is greater than on any other organ". The factors which may be concerned in this relationship were described by Stokes as cholinergic and gastrointestinal mechanisms, emotional control of the sweat glands, vasomotor reactions, allergic response, dextrose metabolism, endocrine factors, the eczema-asthma-hay fever personality and mental tension or fatigue. Cohen reviews the application of some of these factors to acne with particular reference to the mental state resulting from the patient's wish to be rid of a dirty skin and the relationship to sex life. It has often been recognized that acne will clear on marriage. With the intention of testing these various conceptions, Cohen took a group of 60 men with clinical acne and persuaded them to do the mosaic test. A control group of 30 men without acne also did the test, which consists of standardized mosaic pieces comprising squares, diamonds and triangles, each piece being available in 6 colours, which the patient builds into a design of his own choice. Lowenfeld reported on the results and stated that no significant differences could be found between the two groups. Fifty people in the Forces, men and women with acne, were interviewed and particulars were taken of their relevant personal history. A considerable number of possibly significant psychogenic manifestations were found, especially among the men and among the older age groups. These results, however, were not controlled and their interpretation is uncertain. Clinical impressions certainly suggested that women in the thirties with acne are neurotic. A likely explanation is that a disorder primarily of somatic origin can later be maintained by psychological factors after the original somatic stimuli have ceased to act.

Clinical picture

Age incidence.—Cohen discusses the incidence and localization of acne, commenting on the fact that although much investigation into the incidence of the complaint in childhood and adolescence has been carried out, little study has been made on its incidence in early adult life. He believes that the generally accepted upper age limit of 30 years for the disease is too low. He investigated a series of women between the ages of 17 and 40 years (average age 21) and divided his cases into those showing a clinical acne (acne visible on simple inspection) and those with slight acne, in which a search for comedones had to be made. The total acne incidence is clinical acne plus slight acne. The site of the acne was also noted. Cohen found, contrarily to other investigators, that acne occurred on the chin about twice as often as it did on other sites, and also that the evidence of clinical acne occurred about half as often as did total acne. For statistical purposes the series was divided into age groups and it was found that the maximal incidence of acne occurred between the ages of 19 and 21 with a steady decline with advancing years, although incidence was still common in the late twenties and early thirties. Cohen also tabulated the ages of 121 men between the ages of 18–44 years suffering from clinical acne and found that 25 per cent were over the age of 25 years, although the biggest age incidence lay between 18 and 23 years.

Cohen, E. L. (1945) *Brit. J. Derm.*, 57, 10.

— (1945) *ibid.*, 57, 48.

ACTINOMYCOSIS

See also B.E.M.P., Vol. I, p. 173; and Cumulative Supplement, Key No. 26.

Clinical picture

Cardiac actinomycosis

Description of three cases.—Cornell and Shookhoff describe 3 interesting cases of cardiac actinomycosis, of which one case simulated rheumatic fever. Actinomycosis is the commonest mycotic infection in man but it is rare to find the heart and pericardium involved. In the

first patient there were severe pain in the praecordium, dyspnoea, cyanosis and hacking cough. Systolic and late diastolic murmurs were found, with enlargement of the liver and a small right pleural effusion. Fever and a slight leucocytosis were noted, haemoptysis occurred twice and, at one time, a pericardial friction rub was heard. Rheumatic heart disease was diagnosed. Later haemolytic streptococcal septicaemia with empyema developed. After death typical actinomycotic masses were found in a small oesophageal diverticulum, and on the walls of the right atrium and the right ventricle. The mediastinum, the lower portion of the right lung and the diaphragm were extensively involved. An unusual feature was the absence of fistulae to the exterior. In the second case actinomycosis was easily diagnosed from abscesses which appeared in various parts of the chest wall. Both lungs, the pericardium and part of the myocardium were infected, although signs and symptoms of cardiac involvement were not found. In the third case extensive involvement of the right lung, the pericardium, posterior mediastinum and diaphragm was found. During life actinomycosis had been discovered in a swelling on the chest wall. A review of the literature shows that involvement of the heart in actinomycosis is rarely diagnosed. It should be considered in every case of pulmonary actinomycosis. The heart may be involved by direct extension of infection from a neighbouring organ, or by metastasis through the blood, the latter rarely produces clinical signs. The clinical manifestation most commonly found in cardiac actinomycosis is congestive heart-failure. It should be remembered that the infection may reach the thorax by way of the oesophagus.

Treatment

Penicillin

Need for prolonged treatment—Walker and Hamilton describe the treatment with penicillin of 6 cases of actinomycosis, in 2 of which there was involvement of soft tissues only, bone involvement in addition in 3 cases and in the one remaining generalized systemic involvement. The chronicity of the condition necessitates prolonged treatment. Only 2 of the 6 cases had been correctly diagnosed before the patients were admitted to hospital. Actinomycosis should be considered in the diagnosis of any chronic cellulitis especially if it is situated in the maxillary region, the finding of the sulphur granules establishes it. Smear and culture are unreliable methods of diagnosis. The authors agree with Cope, Colebrook and others that the fungus may be carried in the mouth and with Henrici's contention that it may be modified in the mouth to a fragmented or bacillary form, rendering identification difficult. Trauma and infection aid growth. Walker and Hamilton think that the tissue destruction, suppuration and overgrowth of fibrous tissue which occur explain the chronicity of actinomycosis. Most of the cases reported on had previously been treated with radiotherapy, potassium iodide or sulphonamides but the administration of the last named had probably been inadequate, one case unsuccessfully treated by the authors with a sulphonamide was later treated with penicillin and is included in the present series. The authors contend, with Herrell, that penicillin treatment of actinomycosis must be prolonged and they also advocate the resort to surgery. Lomatous tissue was performed in 2 cases with primary healing. The authors suggest a combination of penicillin and sulphonamides as probably the best treatment but did not use it in this series because they were testing the effect of penicillin alone, although sulphadiazine was later administered to 2 patients. The time that has elapsed since treatment has been too short to permit the making of a claim that permanent cures have resulted.

Cornell, A., and Shookhoff, H. B. (1944) *Arch intern Med*, 74, 11.
Walker, J. M., and Hamilton, J. W. (1945) *Ann Surg*, 121, 373.

ADIPOSIITY

See also B E M P, Vol I, p 202

Treatment

In children with hypogenitalism

Thyroid, gonadotrophin and testosterone therapy—A series of children with various degrees of hypogenitalism, cryptorchidism, pseudo-Frolich's syndrome, obesity, growth deficiency and mental retardation has been studied by Finkler, Furst and Klein, who record the influence of hormone treatment on bone growth and development. Prior to, during and after therapy, routine x-ray studies of the skull, sella turcica and long bones were made at regular intervals. The skeletal age was estimated by the epiphyseal development of the distal ends of the radius, ulna and metacarpals and of the phalanges of the hands, by the presence of the centres of ossification, and by the number of carpal bones. The progress of skeletal development was judged in accordance with the standards of Todd and the degree of mineralization was estimated. The authors state that thyroid therapy tended to improve bone density and epiphyseal union, more particularly the former, and was most effective when there had been pre-existing thyroid deficiency. Before treatment, 6 of the children in this group had delayed epiphyseal union and 4 had decreased structural density. Density became normal in all the children after treatment but delay in epiphyseal union continued in 5 of them. Administration of extracts of the anterior lobe of the pituitary gland did not produce conclusive changes in skeletal growth and development in the majority of the patients. In 11 children with delayed epiphyseal union, no effect was produced on bone maturation and the epiphyses remained ununited. Children on this treatment, however, did show improvement in general vitality and mental alertness. Treatment with both chorionic gonado-

trophin and testosterone compounds stimulated bone growth in the longitudinal axis but in the majority of cases did not accelerate epiphyseal union, bone maturation or density. With both treatments there was a general improvement in genital development, mental alertness and muscular tone. Thyroid substance was used in 18 cases, anterior pituitary gland extracts in 25, chorionic gonadotrophin in 19 and testosterone compounds in 18 cases. Before hormone therapy all of the children had various psychological maladjustments or behaviour problems. In cases in which the hormone treatment caused improvement in growth and in genital and muscular development there was coincidental improvement in mental and emotional stability.

Importance of diet

Danowski and Winkler review the complications and treatment of obesity. The analysis is based on an investigation of 141 cases. It was found that obesity is not common after the sixth decade and that the presence of diabetes mellitus is not an aetiological factor. The condition is correlated with a decreased expectation of life and is associated with a great incidence of varicose veins, pains in the joints of the lower extremities and disease of the gallbladder and cardiovascular system. All these disorders tend to appear at a comparatively early age in obese patients. Varicose veins occurred more often in male patients, so that pregnancy cannot be the basic factor responsible for the predominance of this complication. Hypertension is common and, in 12 cases, the systolic blood pressure was decreased by at least 20 millimetres of mercury as the weight fell. A gain in weight, however, rarely caused a rise of blood pressure. If permanent reductions of 30 pounds or more are considered to be significant in patients who weighed 200–484 pounds, treatment produced successful results in only 20 per cent of cases. Failure in the majority of cases must be attributed to an inability to produce a lasting change in the dietary, for many of the patients are housewives constantly exposed to the temptation of food. Evans advocates a limitation of intake to a diet yielding 500 calories daily, but this method can be used for comparatively brief periods; a restriction of calories to about 2,000 daily offers a rational alternative plan. The diet prescribed is sufficient to produce a small negative calorie balance. It is more important, however, to change the nature of the diet than to alter the number of calories. Moreover, increased exercise and medication with desiccated thyroid gland are ineffective procedures.

Benzedrine sulphate

Albrecht reports on a series of cases of obesity treated with Benzedrine (amphetamine) sulphate in doses of 10–30 milligrams daily for periods of 2–8 weeks. He states that nearly all patients taking the drug lose their propensity for eating between meals and before retiring. The weight loss, which averaged about 4 pounds weekly in his patients, is not permanent but can be maintained by a special diet of 450–1,500 calories. During treatment, however, the patient is able to adjust his abnormal appetite to a new level. Contra-indications to Benzedrine sulphate therapy are hypersensitivity to epinephrine (adrenaline)-like compounds, coronary and other cardiac conditions in which vasoconstrictors carry risks, excitability and insomnia. The mode of action of the drug is not entirely clear. It apparently relaxes the stomach, increases pyloric tone and increases gastric acidity. There are no consistent effects on the small intestine or colon. It may produce dryness of the mouth, headache, palpitation, euphoria, coldness of the extremities, insomnia and loss of appetite. Changes in basal metabolic rates are not significant. Recent studies suggest that obesity is not caused by lessened expenditure of energy in the basal state and that no internal secretion is capable of so changing metabolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow. Continuous gain in weight, therefore, suggests an appetite beyond the needs of growth, maintenance and energy. It is presumed that Benzedrine acts largely by controlling appetite.

Albrecht, F. K. (1944) *Ann. intern. Med.*, **21**, 983.

Danowski, T. S., and Winkler, A. W. (1944) *Amer. J. med. Sci.*, **208**, 622.

Finkler, Rita S., Furst, N. J., and Klein, M. (1944) *Radiology*, **43**, 346.

ADRENAL GLAND DISEASES

See also B.E.M.P., Vol. I, p. 232; and Cumulative Supplement, Key No. 30.

Adrenal hypoplasia and insufficiency

Addison's disease

Treatment by the implantation method.—Kemper describes the treatment of Addison's disease by the implantation of normal suprarenal glands or a potent extract of normal suprarenal glands, a method which is desirable in order to avoid the disadvantages, including high costs, of daily injections and of oral administration. It must, however, be borne in mind that accurate diagnosis and determination of the individual patient's daily requirement of the hormone are essential. Neurasthenic and chronic nervously exhausted patients do not, in general, benefit from the treatment. Clinical response to injections of desoxycorticosterone (desoxycortone) acetate, considered with the classic 4 symptoms, justifies the use of implantation treatment. Radiological examination of the suprarenal glands sometimes reveals calcification which, however, may be marked in mild cases or absent in patients with a very high degree of insufficiency. The Kepler-Power water test is safe and useful as a routine measure in diagnosis; the Cutler-Wilder test of the urine chloride concentration when a diet poor in sodium chloride and rich in potassium is given for 54 hours, is useful in difficult borderline cases but is too drastic for routine use. Low levels in fasting blood sugar and flat glucose

tolerance curves are merely suggestive. Estimation of reduced urinary excretion of 17-keto-steroids the author considers to be beyond the resources of the average clinical laboratory. In order to determine daily hormone requirement 3 grammes of sodium chloride should be given daily, in doses of 1 gramme 3 times a day, either as enteric coated pills or tablets or in a flavoured aqueous solution. A daily subcutaneous injection should then be begun of 1 cubic centimetre of an oily solution of desoxycorticosterone acetate (5 milligrams of the steroid compound). Rapid increase in weight or the presence of pitting oedema indicates that an immediate reduction of the dose by half is necessary. The appropriate daily dose is assessed by trial and error and by careful estimation of the wellbeing, weight, strength and vascular tone of the patient. Oedema, hydraemia, cardiac dilatation, dyspnoea and unusual irritability are danger signals of overdosage. Percortin (Percorten) is sold in 125 milligram sterile pellets which, implanted under the skin, each afford to the patient approximately 0.5 milligram of hormone in 24 hours. Thus the implantation of 10 pellets would meet the requirements of a patient needing 5 milligrams of the steroid compound daily. Under local anaesthesia, through a transverse incision in the infrascapular region in the mid clavicular or posterior axillary line, the pellets are implanted in the subcutaneous tissue at least 2 centimetres from the site of incision. They should, theoretically, be effective for 250 days.

Incomplete syndromes

The Waterhouse Friderichsen syndrome—The Waterhouse Friderichsen syndrome is typically a short fatal illness characterized by stupor, cyanosis, pallor, vomiting and a rapidly spreading purpuric eruption. There is a bacteraemia due in the majority of cases to the meningococcus, and at necropsy there is seen to be massive bilateral adrenal haemorrhages. D'Agati and Marangoni have observed 6 cases of the syndrome, including one with recovery, and they report the clinical, pathological and laboratory findings. Of diagnostic significance are a petechial eruption rapidly becoming purpuric, severe shock, facial oedema and anuria of 24–36 hours' duration followed by marked oliguria. The urine shows fixation of specific gravity, albuminuria, haematuria or cylindruria. There is marked leucocytosis. The meningococcus can usually be isolated by culture and in some cases by peripheral blood smear. Renal failure produces elevation of the blood non protein nitrogen and creatinin and there is elevation of the blood sodium and diminution of the blood potassium. Treatment must be directed towards shock, toxæmia and bacteraemia and the adrenal pathology. It involves therefore the administration of fluids, plasma and antimeningococcal serum, chemotherapy by sulphonamides, notably sulphadiazine, and adrenocortical hormone therapy. The value of the latter is, however, questionable. There appears to be two stages in the Waterhouse-Friderichsen syndrome. The first is that of toxæmia associated with shock and circulatory collapse and the second that of hepatorenal failure. Most of the cases have occurred in children but there have been many additional reports of the syndrome in adults, especially in areas in which there has been a general increase in meningococcal infections.

Liver function and the Waterhouse Friderichsen syndrome—Weinberg and McGavack report on a case of Waterhouse Friderichsen syndrome with recovery in which appraisal of liver function was attempted. The incidence and mortality of the syndrome seem to be greatest in patients under 9 years of age. Aetiology is at present unsettled but meningococci have been very often recovered from blood and spinal fluid. Before sulphonamides and potent adrenocortical preparations were available, prognosis was hopeless. Some form of sulphonamide was administered to all of 12 patients who recovered, amongst whom those who also received antimeningococcal serum apparently responded no more quickly than did those receiving sulphonamides alone, the importance of adrenal cortical hormone is emphasized by a case of Haass which despite adequate sulphonamide therapy but without administration of hormone, had a fatal issue. Of 12 recovered patients 10 received watery extracts of adrenal cortex, 2 received desoxycorticosterone acetate (desoxycortone acetate) alone, the drug was administered in conjunction with watery extracts of cortex to 4 patients. The authors consider that desoxycortone maintains tissue and circulation equilibrium, stabilizes blood pressure, stimulates carbohydrate metabolism and leads to early improvement in mental status. All the patients who recovered received liberal quantities of intravenous glucose and saline. The patient individually reported on by the authors was a 63 year-old woman who collapsed at work after having a sore throat for 3 days and a mild headache the evening before she was admitted to hospital. On admission she had a temperature of 102° F, a history of purpura and cyanosis. Treatment consisted of administration of sulphadiazine, intravenously, and of oxygen. Digitalis was administered on account of the age and toxic condition of the patient.

Disorders of function

Blood changes

Effect of stimulation and of adrenalectomy—White and Dougherty describe experiments in which mice were injected daily with 1 milligram of adrenotrophic hormone. The blood changes resulting from these injections included an increase in haemoglobin, erythrocytes and polymorphonuclear leucocytes. It is possible that repeated injections of hormone eventually stimulated the production of erythrocytes in an effort to compensate for the diminution of these cells due to a single dose. There was a persistent absolute lymphopenia,

but no alteration occurred in the total number of leucocytes. In other experiments on mice, removal of the suprarenal glands caused haemoconcentration, absolute lymphocytosis and decrease in the production of polymorphonuclear leucocytes. The erythrocyte counts were not increased despite the reduction in plasma volume. The haemoconcentration was less intense after the animals were given daily injections of desoxycorticosterone (desoxycortone) acetate. Adrenalectomy in the rat did not result in haemoconcentration. On the other hand, there was a significant increase in polymorphonuclear leucocytes. It is concluded that the pituitary adrenotrophic hormone exerts a trophic influence on the adrenal cortex to maintain a physiological control over the numbers of circulatory erythrocytes and lymphocytes. Alterations in the quantity of these cells may be due to a wide variety of unrelated stimuli. This observation should be correlated with the fact that the same stimuli may bring about the secretion of the adrenotrophic hormone. Chronic stimulation of the adrenal cortex need not necessarily give a lymphopenic picture, for continuation of the stimulus initially resulting in a lymphopenia may eventually cause a lymphocytosis.

D'Agati, V. C., and Marangoni, B. A. (1945) *New Engl. J. Med.*, 232, 1.

Kemper, C. F. (1945) *Ann. intern. Med.*, 22, 161.

Weinberg, L. D., and McGavack, T. H. (1945) *New Engl. J. Med.*, 232, 95.

White, A., and Dougherty, T. F. (1945) *Endocrinology*, 36, 16.

ALCOHOLISM

See also B.E.M.P., Vol. I, p. 280; and Cumulative Supplement, Key No. 36.

The toxic effects of alcohol-

Acute alcoholism

Early signs of delirium tremens.—Chapman, writing on delirium tremens, states that an incipient as well as an acute stage should be recognized. Sleeplessness, tremor and apprehension characterize the former, which passes into a state of mental confusion before the active condition of delirium and visual hallucination develops. From experience, patients may often recognize the symptoms of the incipient stage and seek treatment, and then full development of the active stage may be prevented by frequent subcutaneous injections of Luminal sodium (phenobarbitone soluble) (3–5 grains). The main object in treatment is to induce sleep as soon as possible, and the drug usually given is paraldehyde. Inadequate doses may be worse than useless. In the active stage an initial oral dose of from 8 cubic centimetres to 16 cubic centimetres should be given, followed as necessary by doses of from 8 to 12 cubic centimetres every hour. If the oral route is impracticable, paraldehyde may be given intramuscularly in doses up to 10 cubic centimetres. Given intravenously it may be dangerous. Intravenous injections of barbiturates are not recommended for general use, although in wildly delirious patients a solution of Evipal sodium (soluble hexobarbitone) given intravenously has been found to be effective. Morphine is not now given. There is a popular fallacy that abstinence from alcohol may precipitate an attack, but its administration as a beneficial measure, either preventive or therapeutic, has no basis in fact. Spinal drainage and dehydration have had a trial as a means of treatment, but now full hydration up to 3,000 or 4,000 cubic centimetres a day is regarded as promoting a useful sedative effect. Gross malnutrition often accompanies chronic alcoholism as a precipitating factor in delirium tremens, and as these patients are usually subject to severe avitaminosis, they should have generous quantities of vitamins. It has not yet been established with certainty that thiamine hydrochloride (aneurine hydrochloride) and nicotinic acid have a curative effect in developed cases of delirium tremens.

Effect on the motorist.—Smith emphasizes the difficulties inherent in arriving at conclusions about the influence of alcohol consumption on the incidence of road accidents. He is of the opinion that the effect of alcohol has been exaggerated, although a driver's skill may be much impaired by ingestion of a quantity of alcohol which might not render him obviously and certifiably, as laid down in the Road Traffic Act (1930), "under the influence of drink or drug to such an extent as to be incapable of having proper control of the vehicle". Medical examinations are often made after an interval during which the effects of alcohol upon a motorist have greatly diminished. Out of 172,965 accidents in which drivers, cyclists and pedestrians were involved in 1936–1937, only 0.8 per cent was attributed to the effects of alcohol upon either driver or pedestrian, in only 0.3 per cent was the driver inculpated and in only 25 fatal accidents during that year were the drivers held to be "under the influence of alcohol". It can be assumed, however, that not all "drunken" motorists are convicted. One cannot ascertain, by any ordinary clinical test, whether a small but dangerous quantity of alcohol has or has not been imbibed. Under the laws of some States in the United States of America, "if the ability of a driver has been lessened in any degree by the use of intoxicating liquors, then the driver is assumed to be under the influence of intoxicating liquor". Observations in America by Holcomb in 1938 showed that 47 per cent of drivers involved in accidents had been drinking; of these, 25 per cent had 0.1 per cent and 14 per cent had 0.15 per cent or over of alcohol in their blood. Twelve per cent of a general cross section of 1,750 drivers, examined at different periods of each day and night, had been drinking. At a blood concentration of alcohol of 0.15 per cent the majority of people are intoxicated.

Chronic alcoholism

Electroencephalographic and clinical features.—Greenblatt, Levin and di Cori made a study of the electroencephalograms and clinical features of 157 patients admitted to Boston Psycho-

pathic Hospital, during the years 1939-1944, with chronic alcoholism, with or without psychosis, special attention was paid to associated epilepsy. The electroencephalograms were recorded with a Grass 6-channel amplifying system, and the records were classified as normal, borderline, or abnormal. Two hundred and forty nurses, physicians, medical students and hospital staff, 90 per cent of whom were between 20 and 30 years of age, were used as controls, and 10 per cent of abnormal electroencephalograms were found among them. In chronic alcoholics electroencephalogram abnormality was found to increase with age. A greater than normal incidence of abnormality occurred in chronic alcoholics with psychosis, the highest rate of incidence being among those with deterioration or Korsakoff's syndrome, whereas in chronic alcoholism without psychosis no significant abnormality was found. A relatively low incidence (17 per cent) of abnormality was found in 24 patients with "rum fits" who had a negative family and past history for epilepsy, and whose seizures occurred only in association with alcohol. A relatively large incidence (75 per cent) was found, however, among patients with idiopathic epilepsy in whom the onset of seizures occurred at comparable ages with those of patients who had "rum fits". The latter, in spite of the occurrence of seizures, have not the same inborn epileptic predisposition as have idiopathic epileptics. Paroxysmal dysrhythmia was not found in 5 patients with pathological intoxication, although 3 of them had abnormal electroencephalograms.

Treatment of the alcoholic

Medicinal treatment and institutional control

Conditioned-reflex treatment and parole—Thimann describes the use of a part-time protective environment with parole for work as a help to conditioned-reflex treatment and psychotherapy in the treatment of alcoholism at the Washingtonian Hospital, Boston. The patient returns to work while under treatment but spends his free time at the hospital. He is therefore protected during the dangerous times—the evening and the week-end. As he is able to work and earn money and so can at least help to pay for his treatment, he becomes more self-reliant, responsible and self-respecting. It was found that protective environment should be continued for at least a year, supplemented by conditioned-reflex treatment and psychotherapy, social adjustments and, if necessary, relaxation therapy. The Washingtonian Hospital resources are limited, but with suitable grounds in which workshops could be set up, patients who could not be safely trusted to work outside could have the same rehabilitation treatment in the hospital. The success of this system lies in treating the victim of alcoholism as a sick person, which he really is, and as a mature and intelligent individual capable of cooperating in his own rehabilitation.

Non institutional control

The Alcoholics Anonymous Movement in America—Rotman discusses the problem of alcoholism in the United States of America. In times like the present this problem becomes great and there are indications that prohibition may follow the recent war as in 1919 it did after the war of 1914-1918. All alcohol addicts are sick persons and great progress has been made in the medical treatment of their disease, but the psychological aspect has still to be fully investigated. Attempts to classify the alcoholic in any of the accepted categories of abnormal mentality have so far failed, and it is now generally accepted that the alcoholic tends to have an introverted personality which is well displayed by those who prefer drinking in secret. In America the ratio of female to male addicts has risen from 1.4½ in 1931 to 1.2 in 1943 and Rotman asks whether the change is due to the feminist movement. He believes that a close relationship exists between alcoholism and masochism, as exemplified by the common occurrence of association of a male addict with some "doormat personality", such as a widowed mother or, in the case of the female addict, a paramour. The Alcoholics Anonymous Movement includes over 12,000 ex-addicts treated during the past 10 years. Its success appears to rest on the advocacy of good citizenship, social decency and religious principles, which together give the addict a positive goal towards which to strive, instead of on the negative method of pointing out his present degradation. The mentors of the organization are themselves ex-addicts and so have sympathy with the weakness of their disciples. The organization is undenominational, pictures the deity as an energy source and has eliminated the devil from the scheme of things, thus removing one of the worst hallucinations of the alcoholic. Rotman believes that ideally most good would be accomplished by close cooperation between the Alcoholics Anonymous Movement and the medical profession, such cooperation would be an acknowledgement of the fact that alcoholism is a social as well as a medical disease and must be treated as such.

Chapman, C. B. (1944) *New Engl J Med*, 231, 249.

Greenblatt, M., Levin, S., and di Cori, F. (1944) *Arch Neurol Psychiat*, Chicago, 52, 290.

Rotman, D. B. (1945) *J Amer med Ass*, 127, 564.

Smith, S. (1945) *Practitioner*, 154, 205.

Thimann, J. (1944) *New Engl J Med*, 231, 9.

ALLERGY

See also B. E. M. P., Vol. I, p. 302, and Cumulative Supplement, Key Nos. 40-52.

General diagnosis of allergic cases and identification tests

Aetiology and pathology

Aetiological factors—human dandruff—Simon discusses allergic reactions to human dandruff.

He describes an experiment in which skin tests were performed on 50 selected persons, including normal adults and patients with atopic dermatitis, asthma and hay fever, who all were tested with 8 preparations which included combings of dandruff from the scalp, superficial scrapings from normal and diseased skin, and other substances. The object of the experiment was to obtain dandruff-sensitive patients for further investigation. Simon found that extracts prepared from dandruff and to a lesser extent from seborrhoeic dermatitis lesions, caused slight reactions on the majority of skins tested. The other substances gave negative results. In 5 cases of atopic dermatitis the results were positive. Passive transfer to 3 different samples of human dandruff was obtained in these 5 patients. The author thus considers that the work of previous investigators and the results of this experiment have established the existence of allergic activity in human dandruff. In further investigation of these patients for the purpose of establishing the source and nature of the allergen, tests were made against a large number of substances. From this experiment Simon concludes that the allergen is not a constituent of stratified squamous epithelium in general, and does not have its origin in accidental contamination of the dandruff with suspended dust particles. The allergen thus may be the result of some physiological maturation process of the desquamated epithelium of the scalp or may originate from some micro-organism living on the scalp. The experimental finding that the allergen may also be present in the scales of seborrhoeic dermatitis is in agreement with the frequent clinical findings of excessive dandruff in this disease.

Treatment

Specific desensitization.—Cohen and Friedman state that it has been shown that after parenteral administration of histamine-azoprotein, precipitins are formed which are specific in part for the histamine component, and *in vitro* neutralization of histamine can be demonstrated. It was also observed in certain persons so treated that there was a diminution of the whealing response of the skin to histamine. Using the iontophoretic technique the authors have estimated the whealing response of the skin to histamine in 50 non-allergic persons. Serial dilutions of histamine in multiples of two were used. In 45 persons the threshold was at 1 : 6,400,000 and in 5 at 1 : 3,200,000. In 10 cases from a series of allergic patients treated with histamine-azoprotein and similarly tested, the threshold in 8 cases lay between 1 : 200,000 and 1 : 1,600,000 and in only two was it within the normal limits. Cohen and Friedman conclude that the skin can be protected from histamine introduced locally but this is not proof that there would be similar protection against histamine or H-substance produced locally by allergy. Using a similar technique the authors studied the skin wheal produced by eserine sulphate (physostigmine sulphate). The threshold was at 1 : 1,000 in 13 of 15 normal persons and in the other 2 at 1 : 800, whereas in 9 treated patients 3 reacted at 1 : 1,000 and 6 at stronger concentrations. Assuming that the wheal produced by eserine sulphate is similar to that produced by the allergic response, it is concluded that histamine-azoprotein treatment protects the skin against the H-substance which is liberated in the skin, and that thus it would be reasonable to assume that there would be protection against H-substance produced by the allergic response.

General principles.—Bray states that four factors operate in all allergic diseases. Two of these—hereditary predisposition and tissue trauma caused by severe illness—are related to the onset of sensitization. The other two, which are related to the production of the individual attack, are the specific sensitizing substance which may be absorbed into the body by inhalation, ingestion, infection, injection or by means of contact, and the non-specific factor which lowers the production of adrenaline and which operates during illnesses, periods of fatigue and mental or endocrine disturbances. Early administration of adrenaline, which should be repeated in small doses at gradually lengthening intervals, together with an 0.5 grain tablet of ephedrine hydrochloride given by the mouth at 4-hourly intervals, is the treatment for an acute allergic attack. A careful history and, if necessary, routine protein skin tests will usually determine the specific sensitizing substance and the complete avoidance of this by either active removal of or a change in the patient's environment, will prevent recurrences. In cases in which the causative allergen is known, specific desensitization gives extremely satisfactory results; when it is unknown a non-specific protein is worth a trial. Most allergic conditions are associated with a hypochlorhydria and a lowered basal metabolism. For this reason digestive hydrochloric acid and small doses of thyroid extract are often beneficial. Septic foci and any cause of mental anxiety should receive attention. The taking of a well balanced and varied diet by the mother during pregnancy and lactation and the protection of the infant after birth from obvious sources of allergens help to prevent the development of symptoms in the children of allergic parents.

Allergic diseases

Respiratory system

Byssinosis.—Ritter and Nussbaum discuss chronic respiratory problems in the cotton industry. They state that, in Mississippi, industrial dusts from cotton and wood have been classified as inert and nuisance dusts, but that recently the belief has been growing that prolonged exposure to cotton dusts may lead to chronic cough, and to permanent disability—a condition referred to as byssinosis. Owing to the differences in the cottons used and the processes applied the health problems in the United States of America and in Great Britain, respectively, are not necessarily the same. Investigating the cotton industry in Mississippi

the writers found that nearly all mill foremen had had employees who had complained of asthma and the general policy of industrial managements had been to shift such workers to other employment so that they were weeded out of the industry. Of such cases 12 were found and in order to prove the causal relationship between cotton dust and the illness, 2 were exposed in a lint room. In one a very severe attack was precipitated and the other was removed when wheezes were heard in the chest. Physical and radiological examinations of the 12 persons failed to show any abnormality. Examination of 26 employees who had worked for 20 years or more in carding or lint rooms did not bring to light a single case of respiratory disease. Enquiry at the State Tuberculosis Sanatorium failed to discover any patient who had worked in the cotton industry and in whom a diagnosis of bronchiectasis had been made. The authors state that the finding of such occupational asthma was incidental to their general enquiry and that they were of opinion that the longstanding asthma might possibly cause oedema of the lung with fibrosis. One of the 12 cases was of 16 years' duration and the absence of any radiological change was remarkable. Ritter and Nussbaum conclude, from their own personal observation and the consideration of individual cases presented in the available literature, that a belief in byssinosis as a clinical entity is without foundation, and that before such a diagnosis is accepted biopsy or necropsy evidence should be available.

X-ray picture—Jones and Souders report on a case of eosinophilic lung infiltration, a syndrome first described by Löffler in 1932, since when a few cases, in children and in adults, have been reported on. The condition was diagnosed in 13 of 55 demobilized soldiers found by radiography to have lung abnormality. The authors' patient, a 33-year-old married negro, complained of 2 months' fatigue and of cough with wheezing which was worse at night, for 2 weeks, there was sharp pain at times in the right lower thoracic region and a "tired feeling" in the lumbar region. There were impaired resonance and sibilant rales in the left upper lobe. Skiagrams showed infiltration extending outwards from a large left hilar shadow into the mid lung and reaching the periphery in the second intercostal space anteriorly. There was marked eosinophilia. Sputum examination for tuberculosis, tuberculin patch test, 18 inhalant and food allergen tests applied endermically, examination of stools for amoebae and ova, agglutination tests for brucellosis, and trichinosis tests, were all negative. After about 6 weeks' rest at home, but not in bed, the patient ceased to cough and had gained weight, and the lung shadow had disappeared. The aetiology of this syndrome is unknown, it is considered to be a manifestation of allergy of undetermined causation.

Allergy of the skin

The exudative diathesis—Barton and Brunsting describe two cases of Kaposi's varicelliform eruption occurring in adults, although the disease is more often encountered in children. Each patient gave a history of atopic dermatitis, a condition which precedes the disease in 79 per cent of cases. A vesicopustular eruption, associated with localized oedema, appeared on the face and neck. The lesions were accompanied by fever and regional lymphadenitis. Differential diagnosis was required from impetigo contagiosa, herpes zoster generalisatus, dermatitis venenata, varicella and variola. Vaccinia was closely simulated but the virus of this disease was not detected. In this connexion it is of interest that one patient had been vaccinated 4 times. Some observers believe that Kaposi's varicelliform eruption is identical with eczema vaccinatum, a disease which sometimes occurs in eczematous patients exposed to vaccine virus. Tests in one case, however, were positive for the virus of herpes simplex. It is possible that this virus and the exudative diathesis were linked to constitute aetiological factors. Treatment included the application of a dilute solution of potassium permanganate. The internal administration of sulphathiazole was without benefit. Recovery ensued but it is to be noted that reports in the literature indicate a mortality rate of 25 per cent, although fatalities are less common in adults than they are in children. Vesiculopustular lesions developed on the hands of 3 nurses in attendance and it is stressed that the disease can assume epidemic proportions. There is evidence that the eruption appears after an incubation period of 8 days.

- Barton, R. L., and Brunsting, L. A. (1944) *Arch. Derm. Syph.*, N.Y., 50, 99.
 Bray, G. W. (1944) *J. R. Inst. publ. Hlth Hyg.*, 7, 177.
 Cohen, M. B., and Friedman, H. J. (1944) *J. Allergy*, 15, 245.
 Jones, S. H., and Souders, C. R. (1944) *New Engl. J. Med.*, 231, 356.
 Ritter, W. L., and Nussbaum, M. A. (1945) *J. industr. Hyg.*, 27, 47.
 Simon, F. A. (1944) *J. Allergy*, 15, 338.

AMOEBIASIS

See also B.E.M.P., Vol. I, p. 366, and Cumulative Supplement, Key No. 56.

Diagnosis

Protean manifestations of amoebiasis—Morgan describes diagnostic difficulties in amoebiasis the manifestations of which are protean. In bacillary dysentery there may be seen, amoebic and bacillary dysentery may be present at the same time. Amoebae in the stools and dysenteric symptoms may be absent and secondary manifestations may afford the first indication of amoebiasis. Amoebic granuloma in the caecum, at the rectosigmoid junction or in the rectum may cause tenesmus and passage of blood and slime, with or without faeces. The dark red nodular ulcerated lesion may look like a carcinoma and render biopsy essential.

for differential diagnosis even though amoebae may have been isolated from the stools. Late stages of amoebiasis in colon or caecum, leading to palpable tumour, loss of weight and filling defect, present similar diagnostic difficulties; under emetine treatment the mass will not melt away, apparently miraculously, as it does in the early stage, because secondary infection, fibrosis and distortion will be present. Excision of the tumour is then indicated, not merely as a mode of treatment but also because the possibility of carcinoma cannot be excluded. As the lumen of the appendix may be obstructed by amoebic infection and history may be ambiguous, the differential diagnosis between amoebic typhlitis, acute appendicitis and appendix abscess may be difficult. A high mortality rate for operation on uncomplicated active amoebiasis of the caecum and appendix was reported during an epidemic in Chicago but, the author emphasizes, operation must not be delayed if signs of acute "obstructive" appendicitis are encountered within the first 24 or 36 hours, whether the patient has or has not amoebic dysentery. Painful fissures may be due to amoebiasis. The presence of dysenteric infection should be excluded before an operation for haemorrhoids is undertaken.

Treatment

Emetine bismuth iodide and chiniofon.—Manson-Bahr stresses the importance of treating amoebic dysentery with a combination of the two most specific anti-amoebic drugs, namely emetine bismuth iodide and chiniofon. Emetine, when injected, is not to any extent excreted in the faeces and therefore does not come into contact with the precystic forms of the entamoeba. Moreover, the common practice of giving periodic courses of emetine injections tends to produce an emetine-fast strain of *Endamoeba histolytica* and with prolonged dosage toxic effects from the drug are fairly common. Manson-Bahr states that emetine bismuth iodide (E.B.I.) should be given at night in doses of 2–3 grains for 10 nights, each dose being preceded by abstinence from solid food for 4 hours and by administration of a sedative half an hour beforehand. Chiniofon retention enemata, not exceeding 7 ounces, should be given concurrently in the daytime after a light breakfast and a wash-out of the lower bowel. With suitable precautions the solution can be retained for 8 hours. Those who relapse after this treatment can be cleared of infection by a further course combined with protein shock therapy. When E.B.I. is being adequately absorbed, the recipient should experience nausea within about 2 hours and the faeces should be liquid and dark-coloured from the liberated bismuth. Otherwise some failure in absorption must have occurred due to faults in the gelatin or other coat of the capsules or tablets. Manson-Bahr considers that the claims of arsenicals in chronic amoebiasis have not been adequately proved and he criticizes the common practice of giving various drugs in succession haphazardly.

Investigation and treatment of chronic amoebiasis.—Lamb and Royston emphasize the importance of early recognition and thorough treatment of amoebiasis, especially since it may be expected that cases will occur in Great Britain as the troops return from the Tropics. The disease at its onset is mild but it may become chronic and resistant to treatment. Danger to life exists only when a liver abscess is unrecognized and is wrongly treated. Administration of emetine hydrochloride injections has spectacular immediate results in the treatment of the disease, and organic arsenicals and iodine compounds are also of great value. The various drugs and other remedies are usually associated in treatment in varying combinations. The authors record the investigation and treatment of 81 unselected patients, of whom all except 3 had previously been treated and in 44 of whom investigation showed no signs of activity. Active ulceration was found in 34 previously treated cases. During sigmoidoscopy scrapings were taken from ulcers and tested for *Endamoeba histolytica*. Cases suggesting hepatitis were screened and a leucocyte count was obtained. Cases with amoebic dysentery were placed on a 21-day course of treatment, and Auremetine was given by the mouth on odd days and Stovarsol (acetarsol) or carbarsone on even days with a Quinoxyl (chiniofon) retention enema at night and drachm doses of bismuth subnitrate 3 times a day. A full light diet was supplemented by the giving of yeast, ascorbic acid and other vitamins. Twenty-six chronic and 3 fresh cases received this treatment. Except for the 3 fresh cases results were unsatisfactory; the relapse rate after 9 weeks was 91 per cent. The 3 fresh cases were still free from infection 9, 31 and 71 days respectively after treatment. Chronic and previously treated cases tended to relapse soon after the completion of a course of treatment, the percentage of relapse increasing with the time interval. The authors suggest that early and thorough treatment with the remedies used in combination over repeated courses will lessen the number of chronic cases.

Lamb, W. L., and Royston, G. R. (1945) *Lancet*, 1, 455.

Manson-Bahr, P. (1944) *Lancet*, 2, 718.

Morgan, C. N. (1944) *Brit. med. J.*, 2, 721.

AMPUTATION

See also B.E.M.P., Vol. I, p. 378; and Cumulative Supplement, Key No. 57.

General aims and ideals

Satisfactory function of stump

Physical medicine methods.—Dow describes the treatment by physical therapy of soldiers in the Army of the United States as such therapy is practised in hospital amputation centres. In these, after any necessary re-amputation or stump revision, the patient, before being discharged from hospital, is fitted with a temporary prosthesis and in psychologically favourable surroundings is taught how to use it. The combined efforts of surgeon, limb-fitter and

the writers found that nearly all mill foremen had had employees who had complained of asthma and the general policy of industrial managements had been to shift such workers to other employment, so that they were weeded out of the industry. Of such cases 12 were found and, in order to prove the causal relationship between cotton dust and the illness 2 were exposed in a lint room. In one a very severe attack was precipitated and the other was removed when wheezes were heard in the chest. Physical and radiological examinations of the 12 persons failed to show any abnormality. Examination of 26 employees who had worked for 20 years or more in carding or lint rooms did not bring to light a single case of respiratory disease. Enquiry at the State Tuberculosis Sanatorium failed to discover any patient who had worked in the cotton industry and in whom a diagnosis of bronchiectasis had been made. The authors state that the finding of such occupational asthma was incidental to their general enquiry and that they were of opinion that the longstanding asthma might possibly cause oedema of the lung with fibrosis. One of the 12 cases was of 16 years' duration and the absence of any radiological change was remarkable. Ritter and Nussbaum conclude, from their own personal observation and the consideration of individual cases presented in the available literature, that a belief in byssinosis as a clinical entity is without foundation, and that before such a diagnosis is accepted biopsy or necropsy evidence should be available.

X ray picture—Jones and Souders report on a case of eosinophilic lung infiltration, a syndrome first described by Löffler in 1932, since when a few cases, in children and in adults have been reported on. The condition was diagnosed in 13 of 55 demobilized soldiers found by radiography to have lung abnormality. The authors' patient, a 33 year-old married negro, complained of 2 months' fatigue and of cough with wheezing which was worse at night, for 2 weeks, there was sharp pain at times in the right lower thoracic region and a 'tired feeling' in the lumbar region. There were impaired resonance and sibilant rales in the left upper lobe. Skiagrams showed infiltration extending outwards from a large left hilar shadow into the mid lung and reaching the periphery in the second intercostal space anteriorly. There was marked eosinophilia. Sputum examination for tuberculosis, tuberculin patch test, 18 inhalant and food allergen tests applied endermically, examination of stools for amoebae and ova agglutination tests for brucellosis and trichinosis tests, were all negative. After about 6 weeks' rest at home but not in bed the patient ceased to cough and had gained weight, and the lung shadow had disappeared. The aetiology of this syndrome is unknown, it is considered to be a manifestation of allergy of undetermined causation.

Allergy of the skin

The exudative diathesis—Barton and Brunsting describe two cases of Kaposi's varicelliform eruption occurring in adults, although the disease is more often encountered in children. Each patient gave a history of atopic dermatitis, a condition which precedes the disease in 79 per cent of cases. A vesicopustular eruption associated with localized oedema, appeared on the face and neck. The lesions were accompanied by fever and regional lymphadenitis. Differential diagnosis was required from impetigo contagiosa, herpes zoster generalisatus, dermatitis venenata, varicella and variola. Vaccinia was closely simulated but the virus of this disease was not detected. In this connexion it is of interest that one patient had been vaccinated 4 times. Some observers believe that Kaposi's varicelliform eruption is identical with eczema vaccinatum, a disease which sometimes occurs in eczematous patients exposed to vaccine virus. Tests in one case, however, were positive for the virus of herpes simplex. It is possible that this virus and the exudative diathesis were linked to constitute aetiological factors. Treatment included the application of a dilute solution of potassium permanganate. The internal administration of sulphathiazole was without benefit. Recovery ensued but it is to be noted that reports in the literature indicate a mortality rate of 25 per cent, although fatalities are less common in adults than they are in children. Vesiculopustular lesions developed on the hands of 3 nurses in attendance and it is stressed that the disease can assume epidemic proportions. There is evidence that the eruption appears after an incubation period of 8 days.

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 Bray, G. W. (1944) *J. R. Inst. publ. Hlth Hyg.*, 7, 177.
 Cohen, M. B., and Friedman, H. J. (1944) *J. Allergy*, 15, 245.
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AMOEBIASIS

See also B.E.M.P., Vol. I, p. 366, and Cumulative Supplement, Key No. 56.

Amoebic dysentery

Diagnosis

Protean manifestations of amoebiasis—Morgan describes diagnostic difficulties in amoebiasis, the manifestations of which are protean. In bacillary dysentery there may be seen on sigmoidoscopy discrete clear-cut ulcers resembling those produced by amoebiasis and amoebic and bacillary dysentery may be present at the same time. Amoebae in the stools and dysenteric symptoms may be absent and secondary manifestations may afford the first indication of amoebiasis. Amoebic granuloma in the caecum at the rectosigmoid junction or in the rectum may cause tenesmus and passage of blood and slime, with or without faeces. The dark red nodular ulcerated lesion may look like a carcinoma and render biopsy essential.

the occurrence of the two diseases in the same individual. Other theories are based on the presence of gastritis, achlorhydria and achylia. Finally, Teufl believes that therapeutic liver preparations have a carcinogenic effect. This hypothesis remains largely unsubstantiated, despite experiments on mice in which local applications of liver extracts produced skin and subcutaneous tumours.

Other megalocytic anaemias

Secondary megalocytic anaemias

Three cases of megaloblastic anaemia in children.—Davis considers that macrocytic anaemia is a rare condition in childhood and that in some of the previously reported cases a diagnosis of pernicious anaemia could not be upheld on the evidence submitted. He now reports on 3 cases of megaloblastic anaemia in children of (1) 13, (2) 14 and (3) 12 years of age. Based solely on the haematological findings and the morphology of the sternal marrow films, a diagnosis of pernicious anaemia would have been warranted in all 3 cases. In the first case, however, achylia developed 2 years after the onset of the anaemia and there were clear indications of defective nutrition. In the second case hypochromic macrocytic anaemia developed a year after hypochromic microcytic anaemia and there was nutritional dysfunction coexisting. In the third case failure in haematopoiesis was of a temporary nature. In case (1), maintenance of haematopoiesis called for injections of liver extract in a dosage considerably exceeding that required in straightforward cases of pernicious anaemia. The other two cases were completely unresponsive to parenteral liver therapy but were readily amenable to proteolysed liver given by the mouth. Davis suggests that arrested megaloblastic maturation in these refractory anaemias results from a deficiency of some additional haematopoietic factor, present in proteolysed liver but absent—or present only in inadequate quantity—in fractionated liver extracts. In one of the cases described, a coexisting hepatomegaly regressed under treatment with proteolysed liver. Davis suggests that this may have occurred by the haematopoietic virtue of the liver or because its large content of amino-acids, including methionine, corrected the hepatic dysfunction.

Haemolytic anaemias

Sickle-cell anaemia

Associated with cholelithiasis.—Weens reports in detail on 4 cases of cholelithiasis associated with sickle-cell anaemia, of which there are few necropsy reports in the literature. The differential diagnosis of abdominal symptoms occurring in patients with both conditions or with sickle-cell anaemia only, is obviously very important. Attacks of acute pain localized in the epigastrium are common in sickle-cell anaemia and the literature discloses that many such patients have been mistakenly operated on for appendicitis, cholecystitis or ruptured peptic ulcer. The causes of such abdominal crises have not been satisfactorily explained although hepatic infarcts, splenic haemorrhages and nerve root pains due to vertebral changes have all been suggested. It has been established that patients proved to have had both sickle-cell anaemia and cholelithiasis have undergone abdominal crises subsequent to cholecystectomy. (1) Sick-cell anaemia and cholelithiasis, proved by a cholecystogram showing normal filling and 6 calculi, in a 13-year-old coloured male suggest to the author the possibility of increased bilirubin production by a chronic haemolytic process. The erythrocytes in this case ranged between 2,690,000 and 4,350,000 with haemoglobin values from 9 to 10.6 grammes; from 55–95 per cent sickling was observed within 24 hours. The icterus index was 19 and the serum bilirubin 2 milligrams per cent. From the age of 4 years the patient had a history of frequent attacks of pain localized in the epigastrium and left upper abdomen and radiating to the back. These attacks were often associated with soreness between the scapulae and over the sternum and with aching knees and ankles. A younger brother had sickle-cell anaemia. (2) A 24-year-old coloured female suffering from sickle-cell anaemia was admitted to hospital for treatment of a chronic ulcer of the leg. From the age of 13 she had suffered from mild attacks of pain starting around the umbilicus and radiating to the right upper abdomen and back. A cholecystogram showed 5 faceted biliary calculi. (3) A 35-year-old coloured male was admitted for investigation in 1943. He had been proved to have sickle-cell anaemia in 1929 and had been in hospital at intervals for the treatment of ulcers of the leg and for blood transfusions. During these years he had frequent attacks of pain starting around the umbilicus and radiating upwards to the left and downwards to the lower abdomen and the legs. A cholecystogram made in 1931 had shown neither gallstones nor filling of gallbladder but in 1943 an x-ray examination showed there to be many small calculi. (4) In the case of a coloured female, 38 years of age, a chronic ulcer of the leg developed after injury. Examination of the blood showed the presence of sickle-cell anaemia. The gallbladder contained small faceted calculi but was normal in function. Since there was a remarkable absence of abdominal crises and of other abdominal symptoms the case was held to be one of silent cholelithiasis.

Cooley's anaemia

Importance of blood transfusion.—Valentine and Neel believe that it is possible to detect carriers of Cooley's anaemia (erythroblastic anaemia of childhood) with greater accuracy than is possible in any other inherited disorder. Many of the carriers present syndromes which may mimic rheumatic fever, lead poisoning, haemolytic jaundice, anaemia due to deficiency of iron or diseases associated with splenomegaly. Some carriers are constitutionally inferior, with a susceptibility to various infections. Children suffering from Cooley's anaemia

before death and was of varying amount, was found in 196 out of 339 cases. The congo red test was performed in 173 cases, giving a positive result in 87.8 per cent. Albumin was found in the urine in 92 per cent of the 287 cases examined and the loss of albumin caused a tendency towards inversion of the normal albumin-globulin ratio of the serum proteins. As the degree of renal amyloidosis increases the clinical picture of nephrosis may appear and, in the rare cases in which the underlying disease does not prove fatal, death may eventually result from renal insufficiency. Auerbach and Stemmerman state that 100 per cent of their patients who died from this cause showed signs of deficient urinary concentration 3 months before death, in some cases there was also a rise in the non protein nitrogen of the blood one month before death. They believe therefore that evidence of oedema and retention of waste products in a patient with renal amyloidosis must be regarded unfavourably.

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ANAEMIA

See also B E M P Vol I, p 408, and Cumulative Supplement, Key No 59

The megalocytic deficiency anaemias

General considerations

The extrinsic factor and vitamin B complex—Castle, Ross, Davidson, Burchenal, Fox and Ham describe experiments which imply that the extrinsic haematopoietic factor is an unidentified thermostable component of the vitamin B complex which is present in Thomas's "washed casein" and Harris's "water soluble vitamin-free casein" but not in "Labco vitamin free casein" and which can be eliminated by extraction 5 times with cold 65 per cent alcohol and once with boiling 95 per cent alcohol or by repeated precipitation. The authors mention that unpublished work indicated that the extrinsic factor can be removed from beef muscle by repeated extraction with dilute acetic acid but not by autoclaving nor alkalization. Apparently the same procedures eliminate both the extrinsic factor and the known members of the vitamin B complex. The administration to patients with pernicious anaemia of pure vitamin mixtures of individual accessory factors of the B complex together with alcohol extracted or Labco vitamin free casein produced no haematopoietic effect.

Pernicious anaemia

Aetiology

The dietary factor—Askey discusses the dietary factor in the aetiology of pernicious anaemia. He states that three constant findings are present in typical Addisonian anaemia, namely (1) permanent histamine refractory anacidity, (2) permanent reduction of Castle's intrinsic factor and (3) reduction of the stored anti-pernicious anaemia liver principle. A macrocytic anaemia without any or all of these findings is not a true Addison's anaemia and is therefore eliminated from Askey's discussion. There appears to be no connection between malnutrition and the onset of pernicious anaemia. In China, India and Java, where general nutrition may be poor and tropical macrocytic anaemia prevalent, pernicious anaemia is almost unknown, whereas in North America it occurs in 3-4 patients out of every 1,000 admitted to hospital. Little investigation of the diets of patients prior to the onset of the disease has been carried out and no gross evidence exists that presence or absence of any particular food causes pernicious anaemia. In many tropical countries the diet is deficient in protein and vitamins, but although a macrocytic hyperchromic anaemia is common, true pernicious anaemia is very rare. Addison's anaemia does not occur spontaneously in animals and therefore dietary observations in experimental animals are difficult to make. The dog is the only animal in which an anaemia fulfilling the necessary conditions can be produced by a modified diet, but the same diet if given to human beings produces pellagra, not pernicious anaemia. Askey concludes that dietary deficiencies cannot satisfactorily account for the onset of pernicious anaemia, he believes that hereditary factors are responsible for the geographical and racial distribution of the disease.

Diagnosis

Concurrent gastric carcinoma—Kaplan and Rigler state that interest in the coexistence of pernicious anaemia and carcinoma of the stomach dates back to 1878, when Quincke called attention to the association between the diseases. In the present century increasing numbers of case reports have appeared, and several investigations have been conducted to determine whether the two conditions are related aetiologically or merely by chance. The authors examined the data relating to 23,231 necropsies on patients 45 years of age and over. There were 293 cases of pernicious anaemia, and carcinoma of the stomach occurred in 12.3 per cent of these patients. On the other hand, the incidence of gastric carcinoma among all other individuals of comparable age was slightly less than 4 per cent. These statistics constitute conclusive evidence of an aetiological relation between the two diseases. Patients with pernicious anaemia should therefore be examined regularly in order to detect the onset of carcinoma of the stomach. The demonstration of gastric polyps in association with pernicious anaemia is particularly important in view of the apparent precancerous nature of such polyps. Some investigators have suggested that destruction of the gastric mucosa by carcinoma might produce a loss of the intrinsic factor. In very few patients, however, of the great number subjected to gastrectomy does true pernicious anaemia ever develop. The occurrence of one or both diseases in several members of a family has been reported. There is some evidence, admittedly far from conclusive, that hereditary factors may be linked to explain

the occurrence of the two diseases in the same individual. Other theories are based on the presence of gastritis, achlorhydria and achylia. Finally, Teufel believes that therapeutic liver preparations have a carcinogenic effect. This hypothesis remains largely unsubstantiated, despite experiments on mice in which local applications of liver extracts produced skin and subcutaneous tumours.

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transfusion or is the mother of an erythroblastotic infant, is found to have Rh negative blood. The usual method of demonstrating sensitivity is to test the patient's serum for anti-Rh agglutinins. It has been found that there is a large percentage of persons with Rh negative blood who are highly sensitive to the Rh factor yet whose plasma contains no anti-Rh agglutinins. Such cases are explained by the fact that in addition to Rh antibodies which produce haemagglutination there are Rh antibodies which combine specifically with Rh positive cells without producing a visible reaction. If Rh positive blood is mixed with serum containing antibodies of this type, the blood loses its power to agglutinate. The new type of antibody is called the "blocking antibody" and is of clinical significance since it explains the lack of correlation between the titre of anti-Rh agglutinins and the severity of erythroblastosis neonatorum in the infant. The biological test is made by injecting intravenously 50 cubic centimetres of blood to which the patient may be sensitive and comparing the colour of the patient's original citrated plasma with that of the specimen taken 1-1½ hours after the injection has been given. If there is sensitivity the second sample will be distinctly darker and the patient will experience a chill and rise of temperature. Obstetric case histories are given in which there had been abortions, stillbirths and probable haemolytic disease of the newborn. Two cases of this disease are described, in both of which transfusions of Rh negative blood were given. In one case the treatment was a dramatic success, but the other infant, although less seriously ill at first, subsequently died of cholaemia and kernicterus.

Part played by complement—Lubinski, Benjamin and Strean publish observations on 6 cases of haemolytic anaemia of the newborn occurring in 6 families, among which there was evidence that 7 previous infants had had the disease. In all cases, the mother was Rh negative, the father Rh positive (one not being available for testing) and the infant Rh positive. The serum of each mother contained anti-Rh agglutinins, there being no correlation between the latter's titre at parturition and the severity of the disease in the affected infant—that the determining factor in the body is the haemolysin probably explains this finding. Fatal haemolytic anaemia occurred in the first infant of an Rh negative woman, who had been previously immunized by repeated transfusions of presumably Rh positive blood. In order to obviate the danger to potential Rh positive offspring, Rh negative females should not be transfused with Rh positive blood. Another case demonstrated the ineffectiveness and possibly injurious effect of giving a transfusion of Rh positive blood to an affected infant. The treatment of choice is early transfusion of a concentrated suspension of washed Rh negative erythrocytes in saline or inactivated plasma of the same blood group. Maternal erythrocytes thus treated can safely be given if no other donor is available, and should be given in rare cases in which mother and child are both Rh positive or Rh negative. The authors discuss the possible part played by complement in accounting for the relatively slow action of haemolysins in haemolytic anaemia of the newborn, the continued liberation of haemolysins from destroyed erythrocytes until their elimination is completed may explain persistence of haemolysis, which in some cases lasts for weeks.

Summary of present day situation—Witebsky states that Landsteiner and Wiener, in 1940, described experiments in which rabbits and guinea-pigs were injected with the erythrocytes of rhesus monkeys. The serum of the former animals not only agglutinated rhesus monkey cells but also the erythrocytes of 6 out of every 7 human beings. Subsequently, Wiener and Peters reported on 3 cases in which transfusion of blood belonging to the same blood group caused severe haemolytic transfusion reactions. All 3 cases belonged to the Rh negative group and, in 2 instances, the patient's serum agglutinated Rh positive cells. Previous transfusions had been given to the same patients without causing reactions. The severe reactions were due to the re-injection of Rh positive erythrocytes into sensitized patients. Similar reactions were found to be due to the first transfusion in the pregnant Rh negative woman sensitized by her Rh positive fetus. The selection of Rh negative blood is of paramount importance and will prevent haemolytic transfusion reactions in these patients. Further investigations showed that over 90 per cent of all women giving birth to erythroblastotic children are Rh negative, but the children are Rh positive. In some unexplained way the Rh positive cells of the fetus enter the maternal circulation and stimulate antibody production against the Rh factor. These antibodies re-enter the fetal circulation and damage or destroy the child's erythrocytes. The Rh factor of the baby is inherited from the father. Some time is necessary to bring about the degree of sensitization causing erythroblastosis, so that the first pregnancy may be normal. From then on all children may suffer from erythroblastosis provided the father is a homozygous Rh positive individual. If the father is a heterozygote, 50 per cent of his spermatozoa will not carry the gene responsible for the Rh factor and some of the children will be spared the disease. The child with erythroblastosis requires transfusion with Rh negative blood. The mother's blood cannot be used, however, because it contains the Rh antibody which caused the disease. The mother should not nurse the baby, because the breast milk contains Rh antibodies. There is a scarcity of the standard serum employed to determine the presence of the Rh factor, for this serum may become available since sub-types of Rh serum have been discovered which are less likely to cause agglutination. Fortunately, the incidence of sensitization is not great.

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ANAESTHESIA

See also B.E.M.P., Vol. I, p. 472; and Cumulative Supplement, Key No. 60.

Choice of anaesthetic

Physique, condition, age and mentality

Anaesthesia in cases of severe shock.—Crooke, Morris and Bowler investigate the effects of general anaesthetics on a series of 26 patients submitted to major and minor operations whose blood plasma volume was normal, in order to determine the type of anaesthesia best suited to lessen operative mortality in severely shocked casualties. Pulse and respiration rates and blood pressure were recorded at 3-minute intervals, blood plasma volume and haemoglobin being determined at half-hourly intervals. In some cases electrocardiographic records were made. Changes in blood pressure are produced by alterations in depth or type of anaesthesia. With nitrous oxide, oxygen and ether, the effect in deep anaesthesia is variable. With cyclopropane blood pressure rises in proportion to the depth of the anaesthesia. With spinal anaesthesia and with Pentothal sodium (soluble thiopentone), the blood pressure falls. The changes in the blood pressure are not due to any cardiac effects. In operation on patients with traumatic shock, the tendency to fall of blood pressure is much greater. Cyclopropane and oxygen cause a rise in blood pressure except in the severest cases. Nitrous oxide with plenty of oxygen and a minimum of ether is the next best anaesthetic. Deep anaesthesia from ether or chloroform and ether causes a fall of blood pressure. Only when there is considerable haemorrhage during the operation is there a reduction in the blood plasma volume and when this is accompanied by traumatic shock the result may be fatal. It appears that the main effect of anaesthetics on blood pressure is by way of the vasomotor system. It is emphasized that quite severe injuries can occur with little reduction in the blood plasma volume, which may explain why the fall in blood pressure may be less expected. Good anaesthesia in shocked cases demands a minimal amount of an anaesthetic that will stimulate the cardiovascular system, and an adequate supply of oxygen.

The nature of the operation

Tonsillectomy.—Hawksley discusses the means of achieving smooth unhurried anaesthesia for tonsillectomy in children, thus obviating physical and psychological trauma, and describes the procedure in use at the Hospital for Sick Children, Great Ormond Street, London. A glucose drink given 4 hours before operation will lessen postoperative vomiting. Premedication is achieved by paraldehyde, 1 fluid drachm per stone of body weight, as a 10 per cent solution administered rectally 20 minutes before operation or by Nembutal (soluble pentobarbitone) in dosage of $\frac{1}{100}$ grain per stone of body weight, given orally at least 1 hour before operation. Atropine, $\frac{1}{100}$ grain, should be given subcutaneously not less than 30 or more than 40 minutes before anaesthesia is begun in order to avoid excessive secretion during operation. Bronchitis and pulmonary collapse may ensue after badly timed atropine administration. Anaesthesia is suitably induced by ethyl chloride until breathing becomes stertorous, when ether is administered until third plane third stage anaesthesia is reached. On the operating table, anaesthesia is maintained by oxygen bubbled through ether on the Boyle's machine and delivered through a Boyle-Davis gag or hook in the mouth. A sufficient depth of anaesthesia is essential if surgery is not to be hurried and the risk run of damaging the superior constrictor muscle or pharyngotympanic tubes by the adenoid curette. Above 14 years of age, anaesthesia may be induced by nitrous oxide-oxygen-ether, and continued through an endotracheal tube. Pentothal (thiopentone) induction is suitable in occasional cases. For guillotine operations, ethyl chloride will quickly induce a deep anaesthesia lasting for 2 minutes, but neither the operation nor the anaesthetic is recommended. Postoperatively, tongue forceps are left on until the child is actively resenting their presence.

Anaesthesia and the urological patient.—Saklad, Sellman and Howrie discuss some aspects of anaesthesia for the urological patient, whose physiological balance may easily be upset under the stress of anaesthesia and surgery. Some pharmacological effects of commonly employed anaesthetic agents, particularly on renal function, are reviewed. Most satisfactory

minutes. The individual dosage varied considerably. Children required relatively large doses. Three grains of Nembutal (soluble pentobarbitone) were given the night before and 3 hours before operation. One hour before operation, $\frac{1}{2}$ grain of morphine sulphate and $\frac{1}{100}$ grain of scopolamine (hyoscine) hydrobromide were given. Additional doses of morphine may be given during the operation. Oxygen was administered in all cases. In children multiple small doses of morphine were given, which were well tolerated. The average fall in systolic pressure was 12.7 millimetres of mercury. Vasopressor drugs other than the initial injection of epinephrine sulphate were seldom required. Fluids for intravenous transfusion were available in order to treat operative shock should it occur. The incidence of headache after the use of continuous spinal anaesthesia was 3.1 per cent, the headache was of a simple type. In long operations and in vaginal plastic operations an indwelling catheter was always used. No deaths attributable to the anaesthetic occurred in this series.

Rectal anaesthesia and basal narcosis

Basal narcotics

Pentothal sodium—Maidlow describes a method of giving intravenous Pentothal sodium (soluble thiopentone) combined with continuous saline under positive pressure. An upright flat metal bar, 6 inches high, is clamped to an arm rest or table. On the top of this stand is a platform to which a syringe is clipped. Tubing runs from the syringe to a 3-way tap and a needle. Another arm of the tap carries the tubing from a drip bulb and bottle, and a third arm runs to a reserve supply of Pentothal sodium in a gallipot on the stand. The bottle contains saline which is forced through to the tap by means of a bellows. After induction of anaesthesia the tap is attached to the needle in the vein. The syringe on the stand contains a 5 per cent solution of Pentothal sodium—a 2½ per cent solution is employed for weak patients and for cases of shock. The anaesthetic is added in doses of 1–2 cubic centimetres and at intervals which lengthen as the operation proceeds. The total dosage should not exceed 2 grammes and, in long operations, this should be supplemented by anaesthesia with nitrous oxide gas and oxygen.

General

Main available anaesthetics

Comparison of drugs and methods—Elam states that recent advances in anaesthesia have not lowered mortality rates and that the training of anaesthetists is of paramount importance. Ether remains the best anaesthetic and, combined with vinyl ether, is valuable in obstetrics since the latter compound has little effect on the uterine muscle. Postoperative chest complications have been reduced since the adoption of premedication with potassium bromide and chloral hydrate. Anaesthesia with nitrous oxide and oxygen may be complicated by serious anoxia should the amount of oxygen fall below 20 per cent. Mental derangement, fits and death have been reported in such cases. These misadventures are less likely to occur after the addition of some other anaesthetic preferably ether from the Oxford vaporiser. The dangers of chloroform are grossly exaggerated, although it is true that this anaesthetic may produce ventricular fibrillation and necrosis of the liver. Promising results have been obtained by combining local injections of procaine hydrochloride with light inhalation anaesthesia but overdosage of procaine hydrochloride has caused sudden collapse, convulsions and death. In continuous caudal anaesthesia a local anaesthetic is injected through the sacral plications are possible. Trilene (trichlorethylene) must not be used in a closed circuit system owing to the production of poisonous compounds with the soda lime of the carbon dioxide absorber. Cranial nerve palsies and deaths have occurred in these circumstances. Cyclopropane, although a valuable agent, may cause circulatory collapse and cardiac failure, but the addition of helium may prevent allergic reactions. Intravenous anaesthesia with Pentothal sodium (soluble thiopentone) can be maintained for long operations by the use of continuous saline infusions with Griffin's apparatus. It is advisable to give a preliminary injection of a few minims of the drug in order to ensure that the solution is not being injected into an artery.

Anaesthetic convulsions

Predisposing conditions—Williams and Sweet report that clinical observations of 42 cases of anaesthetic convulsions showed that nothing incompatible with an ordinary oxide fit was encountered in any instance. Forty patients had had ether, in most cases in combination with nitrous oxide and oxygen. One death occurred in this series; the patient was a boy who died after the removal of an acutely inflamed appendix. Thus the mortality rate was not greater than might be expected when convulsions of any type supervene in an already ill patient. Electroencephalographic investigations were made in 22 of the cases and the majority of tests were performed from one to two years after the convulsion had occurred. Abnormal findings were recorded in 73 per cent of the cases, and 27 per cent were larval epileptic attacks. Paroxysmal outbursts of abnormal waves were seen in over half the number of patients. The electroencephalograms were found to be similar to those of patients with idiopathic epilepsy. It therefore seems to be clear that an important factor in the aetiology of anaesthetic convulsions is an inborn convulsive tendency. In a patient who is subject to them in other circumstances, convulsive seizures may well develop during anaesthesia. Many of the precipitants of epileptic fits have also been blamed by various authors for precipitating ether convulsions. It is of interest to note that ether, with which anaesthetic convulsions are most commonly associated, produces persistent high voltage abnormally fast activity in

the electroencephalograph during induction. This fast activity is evidence of cerebral hyperexcitability and is one of the concomitants of the epileptic state. Anaesthetic convulsions have been very rarely reported from epileptic institutions. This apparent anomaly is explained by the fact that the epileptic in an institution receives adequate anticonvulsant treatment which inhibits any tendency to convulse during the giving of an anaesthetic. The main difference between subjects of anaesthetic convulsions and of idiopathic fits lies in the degree of predisposition to convulsions.

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ANEURYSM

See also B.E.M.P., Vol. I, p. 501.

Aneurysm of the aorta (thoracic and abdominal)

Aetiology

A blood-borne infection of the abdominal aorta.—Owens and Bass present a case of tuberculous aneurysm of the abdominal aorta which they believe to be the only case reported on as due to blood-borne infection. In 21 previously reported examples the condition resulted from erosion of the aorta by a tuberculous process in an adjacent lymphatic gland and in only 2 of these cases were tubercle bacilli found in the media of the aorta. The chief complaint made by the authors' patient, a 70-year-old white woman, was of intermittent abdominal pain, chiefly on the right side and sometimes radiating to the right shoulder and clavicle. There were intermittent evening temperatures, sometimes as high as 104° F., and occasional rigors. The patient had lost 25 pounds in weight. Individual and family history of tuberculosis were absent. The pulse was thready and the radial artery walls were not thickened. The abdomen was distended and a large, moderately tender, firm and slightly movable smooth mass was felt in the right lateral abdomen. The patient's blood pressure on admission to hospital was 99/66 and fell to 85/55; after transfusion with 500 cubic centimetres of plasma followed by 500 cubic centimetres of isotonic sodium chloride solution, it rose to 140/77. Despite subsequent transfusions, the blood pressure again fell to 82/52. There was increase in the size of the mass in the right abdomen. The patient died on the fourth day after admission. Necropsy showed aneurysm of the abdominal aorta. Sections of the mouth of the aneurysm stained by Gabbett's method showed beaded slender acid-fast bacilli between the elastic tissue fibres of the aorta, transmitted, the authors consider, through the vasa vasorum.

Dissecting aneurysm

Complications

A case of coronary occlusion resulting from dissecting aneurysm.—Wainwright describes a case of dissecting aneurysm producing coronary occlusion. A negress, aged 42 years, during exertion suddenly experienced severe epigastric pain which radiated up to the right arm and back; the pain, which was of knife-like intensity, especially under the scapula, continued for 2 hours, and the patient was then taken to hospital. There it was found that the initial clinical features that day were pyrexia of a few days' duration, leucocytosis, blood pressure 220/125, and a systolic murmur all over the enlarged heart. Syphilis was excluded. Electrocardiograms taken on the first and seventh days showed the sequence of changes diagnostic of recent anterior myocardial infarction. On the fifteenth day, pyrexia, dyspnoea, cyanosis and sweating developed, the blood pressure dropped to 150/60, and an aortic diastolic murmur was heard. Chest pain, absent for the past 10 days, reappeared, most intensely below the right scapular angle. Electrocardiograms now suggested recent myocardial infarction of the posterior wall. Three days later, when the blood pressure was 120/70 and electrocardiograms indicated marked myocardial change, death occurred. At necropsy 50 cubic centimetres of liquid blood were found in the pericardial sac. One centimetre above the aortic sinus was a 5-centimetre-long transverse intimal rent which led to a cavity between the outer and the inner aortic coats and which was produced by a split in the media. Dissection extended down to the aortic ring and along the left coronary artery and its descending branch for 1 centimetre beyond the latter's origin. The lumen of this branch, itself containing no thrombus, was occluded by the pressure of the haematoma in its wall, which microscopically showed separation of the media by the thrombus. A fresh infarction of muscle supplied by the occluded artery was confirmed microscopically. Presented with signs suggestive of myocardial infarction and dissecting aneurysm, Wainwright bases his clinical diagnosis

the latter only on the development of an aortic diastolic murmur which, previously absent, developed in the course of protracted chest pain and sustained hypertension

Cardiac aneurysm

General

Importance of radiology—Delano and Weihe emphasize that radiology has increased precision in the diagnosis of cardiac aneurysm, formerly not often discovered during life. They date the first radiological report confirmed by necropsy to 1927. Of 300 cases reviewed by Platenew in 1926 6 were diagnosed during life and only one of these had been radiographed. Amongst the earliest recorded reports were one of aneurysm of the auricle in 1676 by Borrich and one of aneurysm of the right ventricle in 1796 by Dionis. The authors list coronary thrombosis as the usual cause and abscess of the cardiac wall, trauma, ulcerative endocardial lesions and congenital conditions as rare causes of cardiac aneurysm. Syphilis also is a rare cause but when present appears to be gummatous. About 85 per cent of cardiac aneurysms are situated in the left ventricle, twice as many on the anterior as on the posterior wall. Antero-posterior radiographs usually give sufficient information but the authors emphasize the great importance of screening, citing a case in which reliance upon radiographs alone led to operation on a mass which appeared to be exactly similar to a mediastinal tumour just previously operated on. Upon dissecting out the mass, however, the surgeon was confronted with a cardiac aneurysm for which he performed a successful plastic operation. Careful screening, the authors point out, will usually reveal apical aneurysm which sometimes develops downward into what the French term, picturesquely, *l'ombre hépato-diaphragmatique*. The dilatation of the aneurysmal sac during ventricular systole, termed 'contra pulsatile', Delano and Weihe believe to have been overrated as a diagnostic sign. The average expectation of life after diagnosis of cardiac aneurysm is 2 years and the usual cause of death is not rupture of the aneurysm, despite its thin wall of 1 or 3 millimetres, but recurrence of the form of coronary occlusion which caused the aneurysm.

Delano, P. J., and Weihe, A. R. (1944) *Amer J Roentgenol*, 52, 31

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ANGINA PECTORIS AND CORONARY THROMBOSIS

See also B. E. M. P., Vol. I, p. 547, and Cumulative Supplement, Key No. 62

Angina pectoris

treatment

Suggested method of improving coronary circulation—Amadeo points out that although peasants in Puerto Rico living in the higher altitudes suffer from anaemia, and 80 per cent are infected with uncinariasis (ankylostomiasis) and their diet is deficient in protein vitamins their hearts are capable of sustained muscular effort. A comparison made of individuals of a higher social class, better fed and living in better sanitary conditions tests paradoxically

has a beneficial effect on the heart, especially in the poor patients angina pectoris due to coronary disease. The incidence of angina pectoris, and myocardial pain complained of always disappears as the anaemia diminishes. Patients are examined for presence or absence of haemic murmurs and percentages of haemoglobin. Haemic murmurs, according to Amadeo, should be called functional murmurs of myocardial anaemic anoxia, they are an index of the heart's ability to withstand anaemia. A heart that can withstand severe anaemic anoxia without developing haemic murmurs must be an extraordinarily good heart, and must have been able to develop a special mechanism to the full. This compensation once developed functions throughout later life, withstanding severe anaemia that may occur in old age. The theory is that moderately severe but tolerable anaemia for a sufficient length of time exerts a beneficial effect on the heart by permanently changing the coronary circulatory system into a much more efficient one with total development of the vast reserve of intercommunicating vessels. Absolute verification of this theory would make its application permissible, and would open a promising new road to the prophylaxis of coronary heart disease.

Nicotinic acid—In recent years favourable impressions of the effect of nicotinic acid in the treatment of angina pectoris have been recorded. Stokes points out that nicotinic acid which raises the level of co-enzymes I and II (collectively the V factor) in the blood and tissues, should in theory, assist the removal of lactic acid and other metabolic products which may play a part in causing anginal pain. So far as the ability to produce coronary dilatation is concerned, he does not consider that there is any clear evidence in favour of either nicotinic acid or nicotinamide given by the mouth. Using nicotinic acid in single doses of 50–100 milligrams prophylactically, or in regular doses of 25–50 milligrams up to 200 milligrams daily, and nicotinamide up to 400 milligrams daily on 10 ambulant outpatients with true angina of effort the author found no benefit greater than that which occurred with placebos in either the relief or the prevention of pain. All the cases derived great benefit from glyceryl trinitrate (nitroglycerin). Depression of the R-T segment and inversion of the T wave associated with exercise are commonly accepted as indications of coronary insufficiency. In the case of one patient the giving of 300 milligrams of nicotinic acid was necessary for prevention of R-T depression and pain on exercise, but a severe peripheral flush occurred. This patient could continue pain free exercise until tired when given glyceryl trinitrate. The peripheral effects of nicotinic acid are inconstant even in the

same subject and doses up to 500 milligrams are required to produce such effects with certainty. There are no peripheral reactions with nicotinamide.

Coronary thrombosis

Treatment

Effect of diathermy on coronary flow.—Mart and Miller describe experiments performed on dogs in order to ascertain the effect of diathermy on the coronary flow. In the first experiment a thermocouple was inserted into the musculature of the right ventricle through the opened chest wall. The chest was then tightly closed. It was found that the application of diathermy caused a rise in the temperature of the heart. Eleven dogs were used in the subsequent experiments. A modified Morritz cannula was connected to the cylinder of a piston recorder and was inserted into the coronary sinus. Heparin was employed for the purpose of preventing coagulation. The blood was returned by way of the femoral vein and was kept at a constant rate of flow, temperature and pressure. The blood pressure was recorded from the carotid artery. Seven dogs were given diathermy, with the inductotherm disc applied to the praecordial area. In 6 instances there was an increase in the coronary flow. A similar increase in flow, however, was noted in 2 dogs to which diathermy treatment was not given. Furthermore, the coronary flow was increased to an equal degree in one animal exposed to the heat of an electric light bulb, and in another animal with the inductotherm disc placed over the lower part of the abdomen. It was evident that the changes in coronary flow were caused either by acidosis or by an increase in the blood pressure and heart rate. The authors conclude, therefore, that the application of diathermy does not cause a significant increase in the coronary flow.

Amadeo, J. A. (1944) *Amer. Heart J.*, 28, 699.

Mart, J. A., and Miller, J. R. (1945) *Amer. Heart J.*, 29, 390.

Stokes, W. (1944) *Brit. Heart J.*, 6, 157.

ANTENATAL CARE

See also B.E.M.P., Vol. I, p. 601; and Cumulative Supplement, Key No. 68.

Hygiene of pregnancy

Diet

Effect of protein deficiencies.—Arnell, Goldman and Bertucci, from their investigation of the incidence of protein deficiency among 400 unselected pregnant patients, report that the diets of 18 per cent contained less than half the recommended daily allowance of 85 grammes of protein. Subclinical deficiency was common: nearly four-fifths of the number of patients had a protein intake classified as fair or less than fair. Less than 10 per cent had excellent diets. Much less exact information resulted from study of the possible effects of deficient protein intake on mother and child. A significant relationship was usually observed between the serum protein concentration—also the haemoglobin content—of the blood at term and the protein intake during the latter half of pregnancy. The average values were lowest in the deficiency group, but individual correlation was impossible. The finding that the highest rate of incidence of pre-eclampsia was in the deficiency group supports the authors' previous observations that protein deficiencies may be of aetiological significance in pregnancy toxæmia. Maternal morbidity in the deficiency group was 5 times that in the excellent group. Fetal mortality, but not birth weight, also bore a significant relationship to maternal protein intake. Eleven cases of massive oedema, occurring during the last trimester, were due to a basic protein deficiency, as judged by absence of cardiac or renal disease, pregnancy toxæmias and mechanical or inflammatory factors, and by a minimum loss of weight of 15 pounds from the commencement of treatment to the date of delivery. Gross oedema of the vulva was a most striking feature. The blood serum protein concentration was low in all 11 patients, only one of whom had a protein intake above the minimum subsistence level. Complete recovery ensued on a regimen the basic principle of which was reparation of the protein deficiency by transfused blood, which also corrected the accompanying anaemia, and by subsequent plasma transfusion.

Exercise

The pregnant employee.—Eastman discusses the abuse of rest in obstetrics (1) as it affects industrial workers and (2) as exemplified in spaced pregnancies. About a quarter of a million American women industrial workers become pregnant each year. American observers argue that it is feasible safely to employ pregnant women under certain conditions, notably sufficient antenatal care and periods for rest, no night shifts, heavy lifting or continuous standing and at least 6 weeks' leave before delivery. This was borne out by British observers both during the war of 1914–1918 and the recent war. Yet the policy amongst 50 per cent of American firms which have special arrangements for pregnant employees is to dismiss a pregnant woman, on notification or discovery of the pregnancy, either instantly or within the first 3 months. This policy, besides excluding skilful workers, leads to concealment of pregnancy—whereby antenatal care is forfeited—or even to attempts at abortion, and encourages the use of contraceptives at a time when the birthrate should not diminish. The belief that pregnancies should be spaced by at least 2 years has become almost an axiom of maternity. Findings based on a series of 5,000 cases and one of 33,000, show that infants born during the second year after a previous pregnancy have as small a stillbirth and neonatal rate and as great an average birth weight as have those born after longer intervals. The longer the interval between births, the greater is the risk of development of, or of

appendix that does not show up with efficient x-ray technique, repeated if necessary, may be regarded as pathological. Of 1,000 cases diagnosed as appendicitis, in 22.6 per cent the appendix was not visible. Reflex signs, pain, pylorospasm and ileocaecal spasm elicited or seen in x-ray examination are of value since they indicate active inflammation of the appendix.

Tumours of the appendix

Carcinoid tumour

Three cases of primary carcinoma.—Chomet describes 3 cases of primary carcinoma of the appendix. The first patient, a man aged 40 years, had an appendix—the middle third of which was obliterated—containing pus. Microscopical examination of the middle third showed the presence of adenocarcinoma. In the second patient, a woman aged 22 years, the appendix was removed incidentally at the time of a hysterectomy. The wall of the appendix showed carcinomatous changes of the mucinous transitional cell type. The third patient, a man aged 65 years, was found to have peritonitis and a ruptured appendix, with carcinomatous masses at the base of the organ and in the outer wall of the caecum. Many authors have not distinguished clearly between carcinoma of the appendix and carcinoid tumour. Carcinoma of the appendix occurs comparatively rarely, is observed principally in the fifth and sixth decades and attacks the proximal half of the organ. Carcinoid tumours are usually found in females in the third decade of life. It is stated that 75 per cent of carcinoids occur in the distal fourth of the appendix. The carcinoids are small firm yellow circumscribed nodules but the characteristic carcinoma of the appendix is a glandular mucinous tumour.

Chomet, B. (1944) *Am. J. Clin. Path.*, 14, 447.

Gomez, G. E. (1944) *Amer. J. Roentgenol.*, 52, 624.

ARRHYTHMIA

See also B.E.M.P., Vol. II, p. 10; and Cumulative Supplement, Key Nos. 78–85.

Tachycardia

Simple tachycardia

Hyperthermia and the effort syndrome.—Flickman discusses hyperthermia as a sign in neurocirculatory asthenia. He describes observations on 30 young soldiers all suffering from neurocirculatory asthenia as manifested by fatigue, dyspnoea on slight exertion, palpitation and praecordial pain, facial flush, cold wet hands, labile pulse, dermatographism, tremor of outstretched hands and inability to refrain from respiration for 35 seconds; there were no indications of organic disease. Hyperthermia is defined by the author as an oral temperature of 99.2° F. or above on more than 3 occasions during 10 days' observation. Careful and detailed laboratory electrocardiographic and radiological investigations were made and infection was excluded. In all 30 patients no hypothermia was ever observed but 11 of them displayed hyperthermia, episodic in character and with an average daily range of 2.2 degrees, as contrasted with a daily range of 1.5 degrees and 1.4 degrees in normal and tuberculous patients respectively. When febrile, each of the hyperthermic patients displayed intense localized perspiring of hands, feet and axillae, whilst the skin of the extremities was cold and showed purplish mottling. These signs were absent in tuberculous patients during febrile periods. Four of the 11 patients who were observed for over 110 days showed neither permanent subsidence or progression of fever nor any evidence of physical deterioration. Both febrile and afebrile neurocirculatory asthenic patients displayed symptoms and signs of equal severity. Various psychological stimuli, epinephrine (adrenaline) hydrochloride, amphetamine sulphate, caffeine citrate and typhoid vaccine, all caused in these patients a pyrexia which neither potassium bromide nor sodium Amytal (the sodium salt of isoamyl-ethylbarbituric acid) prevented or reduced. The fever and accompanying signs are presumed to be due, in these patients, to abnormal hypothalamic activity.

Auricular flutter and auricular fibrillation

Auricular flutter

Association of auricular flutter and paroxysmal tachycardia.—Recent publications have drawn attention to the lack of absolute criteria for the differentiation of auricular tachycardia and auricular flutter. Evans maintains that during paroxysmal tachycardia it is not possible on clinical grounds to determine the nature of the auricular arrhythmia, although flutter is favoured if the attack is prolonged. Gradually, however, more similarity than disparity has been noticed between the conditions, both clinically and cardiographically. The most striking contribution has been the finding by various investigators of A–V dissociation in auricular tachycardia. This sign was formerly regarded as typical of auricular flutter, but the distinction can no longer be drawn. Evans records 73 cases of other authors and 27 of his own in which A–V dissociation occurred in auricular tachycardia, and he maintains that if it is confirmed by future cardiographic investigation in the present series of cases, the terms paroxysmal tachycardia and auricular flutter will become interchangeable. Auricular flutter, the author suggests, is paroxysmal tachycardia in which a moderate auricular rate of 200–260 facilitates the finding of A–V dissociation in the cardiogram, because both auricular waves are separate from the two main waves of the ventricular complex. A greater A–V dissociation from slowing of the ventricular rate shows three or more consecutive auricular waves outside the ventricular complex even at higher auricular rates. Paroxysmal tachycardia is auricular flutter in which the more rapid auricular rate, 260–500, prejudices the recognition of the auricular waves hidden within the ventricular complexes and hinders the discovery of a

2 1 A-V dissociation In such circumstances the comparison of a right pectoral cardiogram made during an attack with a cardiogram made during normal rhythm helps to decipher the nature of the arrhythmia. Prolongation of the attack, response to digitalis and association with heart disease often occur in the first type of disorder, but there are many exceptions.

Lanatosid C—Clinical observation has proved the usefulness of rapidly acting digitalis glycosides in supraventricular arrhythmias, although their mode of action is obscure. Tandowsky describes the prophylactic use of lanatosid C in paroxysmal auricular arrhythmias. By its use the average recurrence frequency of paroxysmal auricular tachycardia and flutter in 8 patients was reduced from 4.2 in a 12-month period to 0.37 in a 15-month period, after giving the drug in full digitalizing dose (1.6 milligrams) intravenously at the outset of an initial paroxysm. The amount of drug used prophylactically did not exceed 0.5 milligram daily in 7 cases and twice that amount in the eighth case. Three of the patients had one recurrence of tachycardia during the period of observation, precipitated in one case by an alcoholic debauch, in the second by discontinuation of the drug for a week, and in the third by laparotomy for gallbladder disease. The recurrences were of short duration and each abated without special medication. Associated cardiac lesions in no way affected the usefulness of the drug, and its only outward effect was the occasional appearance of ventricular premature contractions. Characteristic electrocardiographic changes during administration of the drug consisted in slight sagging of the RS T segment with or without flattening of the T wave. Tandowsky states that in the presence of auricular tachycardia and flutter the effect of digitalis cannot be due to shortening of the refractory period of auricular muscle. The effect must depend upon the nodal action of digitalis or upon some unknown action on the neuromuscular mechanism.

Evans, W. (1944) *Brit Heart J*, 6, 221

Friedman, M. (1944) *War Med*, 6, 221

Tandowsky, R. M. (1945) *Amer Heart J*, 29, 71

ARTERIAL DISEASE AND DEGENERATION

See also B. E. M. P., Vol. 17, Cumulative Supplement, Key Nos. 86-93

The mechanism of the arterial circulation

Classification of peripheral vascular diseases

Main elements of diagnosis—Goetz suggests a classification of peripheral vascular diseases into two main groups, non-organic and organic. He subdivides the non-organic group into vasoconstrictor and vasodilator disorders and the organic group into congenital, inflammatory, non-inflammatory and neoplastic disorders. To appreciate the significance of vascular diseases it is necessary to understand the physiology of the skin with particular reference to heat loss. Blood flow through the skin serves needs which are not exclusively metabolic. Arteries supplying the skin have to be almost completely obliterated before the nutrition of the skin is threatened. Heat, which increases the metabolism of the skin and consequently the demands upon the circulation, is a great danger when marked ischaemia exists and may result in gangrene. In Raynaud's phenomenon the blood flow between the attacks is just enough for tissue metabolism, the decrease being due to the high central vasomotor tone which in turn is the result of the body's need to preserve heat. Similar factors are concerned in hypothyroidism and in anorexia nervosa and the reverse in hyperthyroidism and fevers. In addition to outgoing centrifugal fibres, afferent sensory filaments run in the vascular nerves which are capable of conducting active vasodilator impulses apart from the relaxation obtained by the loss of sympathetic tone. The appearance of the patient may be significant, for example, the anxious countenance of Buerger's disease or the plum colour of polycythaemia may be seen. Xanthelasma palpebrarum will suggest the disturbed fat and cholesterol metabolism of atheromatosis. An expressionless face without natural creases is typical of scleroderma. Colour changes in the extremities are of great importance, for example a dusky red discoloration of the toes is typical of organic vascular disease. Palpation of the main vessels is an essential examination, especially when any surgical interference is contemplated. A case is quoted of gangrene occurring in both great toes after operation for hallux valgus in a patient in whom the pedal pulses were absent. Goetz stresses the value of digital plethysmography in diagnosis and for the assessment of collateral circulation, and of arteriography, using a special long-exposure technique. The medical profession, he states, must realize the possibility of peripheral vascular disease whenever a patient complains of pain or of discomfort in the feet.

Peripheral vascular disorders

Importance of tissue nutrition—In an article on peripheral vascular disorders Learmonth mentions the possibility of ischaemia being present in all such disorders, and strongly emphasizes the necessity of attention to the two fundamental principles in their treatment: control of haemorrhage when present, and the maintenance of tissue nutrition. In the former, the various kinds of ligatures, artery forceps and tourniquets have been used since early times. The surgical closure of vessels was then evolved and more recently the establishment of axial anastomosis has been used. In the maintenance of tissue nutrition transfusion is most valuable. A successful development of this, after the use of dried and liquid plasma, has been the alcohol fractionation of plasma proteins, and the use for transfusion of the albumin only, in a 10 per cent solution. Other proteins have been tried, for example bovine plasma albumin, gelatin and lyophilized but the use of human plasma proteins is, at present, most favoured.

In wounds of large vessels suture is required, anastomosis of severed arteries and the closure of fistulae between arteries and veins or the substitution of various types of cannulae in order to keep up the flow temporarily until a satisfactory collateral circulation is established. Thrombosis is prevented or minimized by the use of anti-coagulants such as heparin and dicoumarin. It has been found that when it is necessary to ligature a main artery of an extremity, a preliminary sympathectomy, which allows alternative vascular channels to dilate, minimizes the risk of massive gangrene, as does also the reduction of the local metabolic rate by the application of cold.

Arteriography

Learmonth² describes the technique of arteriography of peripheral vessels by an opaque medium for the demonstration of the extent of collateral circulation, the site and extent of arterial aneurysms and the site of arteriovenous fistulae. He warns against routine use of arteriography in investigating complications of arterial wounds when clinical examination alone might suffice, and says that familiarity with Makins's monograph will aid to this end. Arteriography may help to decide the surgical approach in lesions of the profunda femoris and the popliteal arteries and in the beginning of the anterior and posterior tibial arteries. The opaque medium is introduced into the common or the superficial femoral artery, according to clinical indications. Spinal anaesthesia—120 milligrams of procaine hydrochloride half an hour before operation—was used so that the vessels should be freed from vasoconstrictor control. For the femoral or the profunda femoris artery the leg is kept straight with slight lateral rotation; for the popliteal artery the thigh is slightly flexed, abducted and everted, and the knee is bent 20°, its lateral aspect supported by a sand bag. Incision is made in the line of the vessel, in the femoral triangle for the profunda femoris or in the subsartorial canal for the popliteal artery. Much disturbance of the artery may cause local spasm, even under spinal anaesthesia. Diodone, 50 per cent, warmed to body temperature, has been used and was injected into the artery from a 10 cubic centimetre record syringe with eccentric nozzle and through a No. 19 needle, inserted bevel downwards and parallel to the artery wall; thus a valvular tunnel was provided which intra-arterial pressure closed when the needle was withdrawn. Before injection all instruments and towel clips should be removed in order to avoid their appearance on the plate.

Periarteritis nodosa

Clinical picture

General review of the disease.—McCall and Pennock believe that periarteritis nodosa is not the rarity that it was once thought to be. The aetiology is unknown but the disease may be allergic or toxic in origin. Syphilis is not a factor. Protean clinical and pathological manifestations were noted in a group of 12 male patients. The bizarre features of the disease depended upon the distribution and severity of the necrotizing arteritis. The onset was insidious and the chief symptoms were anorexia, asthenia, myalgia, fever and loss of weight. Small pleural effusions and terminal bronchopneumonia were observed in many cases. In one instance arterial thrombosis caused gangrene of the appendix. The right superior gastric artery was completely thrombosed in one patient. Arterial changes were found in the coeliac and mesenteric vessels. There were petechiae in the mucosa of the stomach and small bowel. Jaundice occurred in 3 patients but the lesions in the hepatic vessels were insufficient to produce cirrhosis of the liver. Chronic pancreatitis and peripheral neuritis were important manifestations. Moderate hypertension and albuminuria, with hyaline and granular casts, were present in every patient. Nitrogen retention was evident in 60 per cent of cases. Cardiac enlargement and abnormal electrocardiograms were noted in the last weeks before death. The valvular lesions appeared to be similar to those seen in acute rheumatism. The changes in the skin included neurodermatitis, erythema, subcutaneous nodules and necrotic lesions. Blood examination showed a moderate leucocytosis, and eosinophilia was found in 3 patients. The characteristic lesions were in the small and medium arteries and veins. The necrosis was of a fibrinoid nature, affecting the intima and the inner portion of the media. These changes were similar to those seen in rheumatism, malignant nephrosclerosis and disseminated lupus erythematosus. Solomon, Kasich and Kiven describe degenerative, acute inflammatory, granulating and healing phases, but these stages may be seen simultaneously. Palpable nodules and biopsy of a muscle were helpful in the diagnosis of the condition in 3 male adults during life. The disease is encountered in patients of all ages and there is an equal sex distribution. Recovery is rare, for no satisfactory treatment is known.

Complications

Granulomatous lesions.—Lindsay, Aggeler and Lucia report on a case, in a married white woman aged 57 years, of chronic granuloma associated with periarteritis nodosa; there was extensive renal involvement and death ensued. Descriptions of widespread granulomatous lesions associated with periarteritis nodosa are rare. The patient reported on had complained for nearly a year of weakness, pyrexia, anaemia, loss of weight, cough with sputum, and crusting of nasal mucous membranes. Later there was transient swelling of the parotid and anterior cervical lymph glands. There were atrophic rhinitis and saddle nasal deformity. One month after admission to hospital the patient died in coma with a clinical diagnosis of sarcoidosis. At necropsy, 30 minutes after death, a urinous odour was detected when the peritoneal cavity was opened. The kidney cortices were firm, fibrous and light yellow in colour; pyramids were light pink and poorly striated. Microscopically the cortices were

seen to be replaced by fibrous tissue densely infiltrated with plasma cells, lymphocytes and neutrophilic and eosinophilic leucocytes. There were extensive changes in the glomeruli. The convoluted tubules were dilated and hypertrophied and showed cloudy swelling and minimal fatty degeneration of lining cells. Microscopical appearances of the liver after death were normal, but a portion which had been removed surgically 2 months before death, showed signs of a small aneurysm. The nasal cartilage, the posterior lobe of the hypophysis and of the parotid gland all showed signs of a chronic granulomatous inflammatory process. Many histologically healed vascular lesions corresponding to periarteritis nodosa were detected.

Chronic arteritis

Pathology

Effect of age and disease on medial calcification—Blumenthal, Lansing and Wheeler carried out a statistical analysis of specimens from 582 aortas in order to determine the relation of age and disease to calcification of the media. The specimens were removed from the proximal portion of the arch and stained with an alkaline solution of Delafield's haematoxylin and eosin. The preparations revealed calcium as a dark-blue granular material, but the method of micro incineration proved to be of greater value in identifying the more finely dispersed calcium. The studies tend to confirm Ravault's observations that medial calcification is primarily associated with the elastic elements since, in the early stages, calcium is deposited between rather than in the muscle fibres. Examination of various levels through the whole length of 6 aortas indicated that the abdominal aorta undergoes a more noticeable degree of calcification of the media than does the thoracic segment. This may be correlated with the greater extent of intimal involvement in the arteriosclerotic abdominal aorta. In 3 cases it was noted that, within a single aorta, calcification of the media was more intense in the immediate vicinity of intimal plaques than it was elsewhere. It is considered that intimal plaques are a result of medial injury and other localized conditions and that the secondary intimal changes produce the phenomenon of arteriosclerosis. This is supported by the observations that calcification of the media precedes the formation of intimal plaques. Moreover, these plaques do not occur without medial calcification or some other injury to the media. The data show that calcification is not influenced by sex and chronic disease, and is less apparent after the age of 60 years. Of 42 specimens of syphilitic aortitis 33 showed no calcification of the media and only 9 showed it to a very slight degree. Specimens from hypertensive patients between the ages of 30 and 60 years revealed pronounced medial calcification. At present there is insufficient evidence to determine whether or not this is the effect of an existing hypertension or whether it is a factor in the aetiology of the disease.

Clinical picture

Principal signs of arteriosclerosis—Evans, defining arteriosclerosis as "a vascular reaction in terms of structure to a pathogenic stress", differentiates between having arteriosclerosis and suffering from it, and quotes Allbutt's dictum that "arteriosclerosis is not a clinical but a pathological name". He states that in general terms, persistent hypertension is clinical evidence of arteriosclerosis. Certain arteries may be affected whilst others escape. Signs of arteriosclerosis may be present without symptoms and vice versa. The signs are thickened arteries, accentuated aortic second sound, hypertension (except in the senile type), aortic and apical systolic murmurs, radiographic evidence of calcification of peripheral vessels and the characteristic retinal picture. The author emphasizes the element of area angiospasm in arteriosclerotic manifestations and advocates detailed study of the clinical events in intermittent claudication in order to aid interpretation of the symptoms of the disease in other areas, notably in coronary occlusion. Symptoms indicate activity or progress of arteriosclerotic disease and are differentiated under the headings of peripheral, retinal, cerebral, renal and coronary arteriosclerotic disease respectively. The author subdivides the clinical manifestations under those due to changes in structure and those resulting from disordered function, and lists the latter under hypertonia, angiospasm and haemorrhage respectively. A rising or varying blood pressure indicates arteriosclerotic disease and clinical experience suggests that pressures of the order of 240/130 lead to progressive changes whereas sustained pressures of about 200/100 seem compatible with quiescence of the disease and possibly with many years of active life. Local angiospasm may cause symptoms before organic disease becomes evident as, for example, in cases in which nocturnal cramp long precedes intermittent claudication or when various cardiac syndromes such as tachycardia, mild dyspnoea on exertion or cardiac pain occur for years before cardiovascular disease is discoverably evident. Arteriosclerotic disease may cause, through local angiospasm, exudates and haemorrhages, notably in the brain or retina but also in the nasal passages, kidneys, stomach, bowel, lungs and uterus.

- Blumenthal, H. T., Lansing, A. I., and Wheeler, P. A. (1944) *Amer J Path*, 20, 665.
 Evans, G. (1944) *Practitioner*, 153, 129.
 Goetz, R. H. (1945) *S Afr med J*, 10, 91.
 Learmonth, J. R. (1944)¹ *Brit med Bull*, 2, 55.
 — (1944)² *Lancet*, 2, 745.
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 McCall, M., and Pennock, J. W. (1944) *Ann intern Med*, 21, 628.
 Solomon, S., Kasich, M., and Kiven, N. (1944) *Ann intern Med*, 21, 638.

ARTHRITIS: OSTEOARTHRITIS

See also B.E.M.P., Vol. II, p. 91; and Cumulative Supplement, Key No. 100.

Aetiology**Classification**

Two types of spinal osteoarthritis.—Fletcher distinguishes two types of spinal osteoarthritis. Marginal polyspondylitis is characterized by osteophytes arising from the anterior and lateral aspects of the vertebral bodies. Osteophytic formation, as demonstrated by anatomical and pathological evidence cited, occurs in the short deep intervertebral ligaments and its maximum incidence lies at the fourth cervical, the eighth and ninth thoracic and the third and fourth lumbar vertebrae. Predisposing factors include faulty posture, scoliosis, degeneration of intervertebral discs, loss of turgescence of nuclei pulposi, and increasing age. The synovial apophyseal, or posterior spinal, articulations may develop osteoarthritis under certain conditions, including abnormal pressure. Cartilage loss centrally is succeeded by peripheral growth. The maximum incidence is at the seventh cervical, the first thoracic, from the second to the fifth thoracic and from the second to the fourth lumbar vertebrae. The commoner sites of pain, the chief symptom of spinal osteoarthritis, coincide with the outcrops of polyspondylitis, not with those of apophyseal osteoarthritis. Pain felt in the anterior and lateral aspects of the thigh Fletcher considers to be suggestive of lumbar osteoarthritis. Radiographic, in addition to clinical, evidence would favour polyspondylitis as the commoner cause of symptoms. Narrowing of intervertebral spaces with sclerosis of surrounding bone and lipping of vertebral bodies characterize polyspondylitis. Radiographic demonstration of the apophyseal joints requires special technique; nevertheless Fletcher pleads for more frequent requests for their visualization.

Incidence, distribution and predisposing causes

Genetic analysis concerning Heberden's nodes.—Stecher and Hersh discuss the mechanism of the inheritance of Heberden's nodes, and base the investigation upon a mathematical analysis of the pedigrees of 74 affected persons. The affected index cases and their siblings included 127 men and 215 women. The incidence in women was comparatively great, for 108 (one half) were affected. The 1 : 1 ratio suggests that the character depends upon a single autosomal dominant gene. Only 4 males, however, were affected and it is assumed that the condition is recessive in men. Genetic examples are recognized of factors dominant in one sex and recessive in the other, as in the case of hereditary baldness. From the genetic standpoint Heberden's nodes show certain peculiarities which include multiple involvement among female siblings without brothers being affected, transmission through females in a manner to suggest maternal unilateral inheritance and an approximation to the ratio 1 : 1 among the daughters in families in which neither parent is affected. With matings of the Aa × aa type, one half of all children will be heterozygous. The women of this constitution will develop the condition but the men will not. According to this assumption, an equal number of men and women are of the heterozygous constitution and such men may have been the fathers in those families in which no antecedent involvement was known. Furthermore, for a man to be affected, both parents must transmit the character to him but only the mother is likely to show it.

Fletcher, E. (1945) *Brit. J. phys. Med. N.S.*, 8, 45.

Stecher, R. M., and Hersh, A. H. (1944) *J. clin. Invest.*, 23, 699.

ARTHRITIS: RHEUMATOID ARTHRITIS

See also B.E.M.P., Vol. II, p. 74; and Cumulative Supplement, Key No. 98.

Treatment**Medicinal**

Use of bismuth and its salts.—Douthwaite describes the treatment of rheumatoid arthritis with bismuth. Because toxic reaction to gold is very great, he decided to find out whether or not another metal would be as effective in treatment as gold and he chose bismuth because of its low toxicity and its pharmacological similarity to the heavy metals. Twelve consecutive patients with active rheumatoid arthritis were given 2 grammes of bismuth spread over equal weekly injections; 9 were given bismuth metal and 3 bismuth salicylate. Eleven of the patients had had previous gold therapy which had failed in 3; the remainder had relapsed after the end of the course. With administration of bismuth 6 patients lost their symptoms, but in 2 patients the final sedimentation rate was between 7 and 15 millimetres in one hour and they relapsed within 8 weeks. The remaining 6 cases Douthwaite classes as failures; 2 of the patients showed some clinical improvement but their sedimentation rate remained high and unchanged and they relapsed within 7 weeks. In the 3 patients in whom gold treatment had failed, bismuth treatment also failed. There were no toxic reactions. The series was controlled by a group of 6 rheumatoid arthritics who were given injections of sterile water weekly which were stopped after 6 weeks as no objective improvement could be detected. Douthwaite states that it has been shown that bismuth can exert a beneficial effect upon rheumatoid arthritis, but that its effect does not compare favourably with that of gold. In his last 200 cases of gold therapy symptoms and signs of activity were lost in 70 per cent of cases. Relapses occurred earlier than with gold and the author considers that bismuth is unlikely to be of help in a gold-resistant case. He concludes that bismuth should be reserved for rheumatoid arthritics who are intolerant of gold.

Penicillin.—Boland, Headley and Hench report on clinical trials with penicillin given to

10 soldiers with early progressive rheumatoid arthritis. Every 3 hours day and night penicillin was administered intramuscularly in daily doses varying from 120,000 to 320,000 Oxford units. Total doses were from 1,800,000 to 3,250,000 units within 14–20 days. Such dosage is known to be adequate against even severe infections from haemolytic streptococci and *Staphylococcus aureus*. In 7 cases no significant subjective or objective improvement resulted. One patient felt worse, another felt better but showed no objective improvement, and in a third there was moderate subjective and objective improvement in some of the affected joints. Considering the capricious nature of rheumatoid arthritis the authors regard the improvement mentioned as unrelated to penicillin administration. No significant improvement occurred in blood sedimentation rates or in comparative leucocyte counts on synovial fluid. Six patients had better appetite. These essentially negative results, the authors consider, do not support the idea that haemolytic streptococci may be aetiological related to rheumatoid arthritis which, they suggest, is not caused by any of the bacteria already known to be rapidly affected by penicillin. It is concluded that penicillin should not be used for further treatment of rheumatoid arthritis until it is abundantly available, but that further researches with penicillin in the treatment of this disease may be in order. At present the limited supplies available for clinical use should be allotted for the treatment of patients with diseases in which curative results are more likely to eventuate than they are in rheumatoid arthritis.

Boland, E. W., Headley, N. E., and Hench, P. S. (1944) *Proc Mayo Clin*, 19, 505

Douthwaite, A. H. (1944) *Brit med J*, 2, 276

ARTHRITIS: GENERAL

Aetiology

Endocrine imbalance

Influence on treatment of arthritic diseases—Pemberton states that infection, although important, cannot be regarded as the basic cause of arthritic diseases. There is significant evidence for the view that the two groups of arthritides, atrophic and hypertrophic, together with certain other aspects of rheumatism, are at least partly referable to imbalance within the neuro-endocrine chain. Thus it is known that pregnancy has a temporary beneficial influence on the arthritic woman and that menstruation has an exacerbating effect. Many signs and symptoms of arthritis can be attributed to disorders of the endocrine glands. For example, hyperfunction of the growth factor of the pituitary gland produces various manifestations of hypertrophic arthritis such as osteophyte formation, calcification of cartilage, phalangeal enlargement, megacolon, paraesthesia and sthenic build. Selye believes that both hypofunction and hyperfunction of the endocrine glands may elicit disorders of the joints. There is not, however, so much clinical evidence with which to incriminate the endocrine system in atrophic arthritis as there is in the case of the hypertrophic type. The author describes a case of arthritis in which hormonal assays of the urine indicated the presence of multiple imbalance representative of a severe postmenopausal state. Replacement therapy is of value in arthritis due to diminished activity of the endocrine system, as in the treatment of menopausal arthritis by means of oestrogenic substances. In certain instances of endocrine overactivity mild sedation under conditions of complete rest, will aid in restoring equilibrium. The general order of treatment should also include optimal nutrition, psychic re-education, the maintenance of adequate gastro-intestinal function, and medication with iron, arsenic and nux vomica. Optimal nutrition is achieved by means of a high protein diet and ample fat, green vegetables and fruits and some restriction of the concentrated carbohydrate foods. Physical therapy consists chiefly of heat treatment, gentle massage and postural exercises. The patient may require orthopaedic treatment and eradication of septic foci. Simple procedures may initiate convalescence in contrast to heroic measures such as massive vitamin therapy, and injections of gold, vaccines and nonspecific proteins. It is possible that these measures often fail because of the unbalanced and improperly responsive condition of the host.

Pemberton, R. (1945) *Amer J med Sci*, 209, 364

ASTHMA

See also B E M P, Vol II, p 179, and Cumulative Supplement, Key No 110

Aetiology

Specific sensitization

Influence of climate and dust in soldiers—Leopold gives an account of 200 soldiers who returned from overseas service because of asthma severe enough to incapacitate them for further duty. One hundred and thirty-seven patients gave a history of the disease prior to entry into the Army. The onset of the disability was precipitated by climatic factors, dust and infection. In most cases the attacks occurred in those tropical regions characterized by high temperature and excessive humidity. In one asthmatic who had been free from symptoms for years, there developed severe attacks during two periods of constant rain. He was well during hot dry weather and also after leaving the area in which the attacks occurred. Exposure to dust caused the onset of asthma in 16 per cent of cases. One of these patients was a truck-driver who gave no history of allergy. He arrived in New Guinea in the rainy season and was quite well. Later, while he was driving on dusty roads during dry weather, asthma developed, especially when he was exposed to the dust raised by traffic. In 9 cases the onset of the disorder was due to infection but, in 24 per cent of cases, subsequent attacks

were precipitated by infections of the respiratory tract. Climatic factors and dust were responsible for the repetition of the attacks in respectively 88 per cent and 84 per cent of cases. Psychogenic factors were of no aetiological significance. The great majority of patients were skin-sensitive to dust and to feathers; only a minority showed skin reactions to pollens. According to Durham, tropical areas do not have the flora or the climate conducive to the development or spread of air-borne pollens and fungus spores. Treatment included conventional medication and all the recognized procedures relating to allergy, but unsuccessful results were obtained with inhalations of carbon dioxide.

Pulmonary acariasis.—Soysa and Jayawardena discuss pulmonary acariasis as a possible cause of asthma. They describe the investigation and treatment of 30 cases of asthma with marked eosinophilic leucocytosis and characteristic radiological lung signs; the patients showed no familial or pre-existing susceptibility to asthma. The criterion of cure was reduction of eosinophil count, not clinical control. Blood was examined for signs of leucocytosis and eosinophilia and alterations in sedimentation rate and differential counts were made daily by the 1,000 cell count method. Faeces were repeatedly examined for ova, cysts, parasites and Charcot-Leyden crystals. Sputum was constantly examined for *Mycobacterium tuberculosis*. For mites it was examined by the special technique of Carter, Wedd and D'Abrera, which is as follows. The fresh sputum is treated first with an equal quantity of 1 per cent potassium hydroxide; the mixture is shaken and allowed to stand until the mucopurulent material has disintegrated. After a few hours, when the mixture has become more or less clear, 5–10 drops of Löffler's alkaline methylene blue are added and the solution is again shaken. Enough formalin to give a 10 per cent concentration is introduced and the mixture is left for 18–24 hours; it is then centrifuged and the supernatant fluid is drawn off. The deposit is examined under a binocular microscope. In 11 out of 21 sputa thus examined mites of either *Tyroglyphus* or *Tarsonemus* were found. Repeated examination of faeces showed *Ankylostoma duodenale* in 1 case, *Ascaris lumbricoides* in 2 cases, *Trichuris trichiura* in 3 cases, *Blasocystis hominis* in 3 cases and *Trichomonas hominis* in 1 case. Anthelmintic treatment did not produce any reduction in eosinophil count. All the patients under investigation had lived or worked in obviously mite-infested surroundings. Before administration of arsenic, in a form such as carbarsone or Stovarsol, the patients received ineffective routine asthma treatment; they responded, however, to arsenic therapy in the dramatic manner reported on by Weingarten and others.

Morbid anatomy

Age and fatal termination

Comparison of types of asthma.—Rackemann cites a series of 50 fatal cases in which asthma was the presenting symptom which were seen at the Massachusetts General Hospital. Necropsy was performed in all the cases and the findings are recorded in a chart which shows the age of the patient, the duration of the disease and the mode of death. In 27 cases the typical pathology was found: the distended lungs were of a pale grey appearance and on section the cut ends of the bronchi were prominent, the lumen in many cases being filled with a tough sticky material. Microscopically, similar plugs were seen in most of the smaller bronchi. In the cases in which the asthma started in earlier life the eventual causes of death included pneumonia, arteriosclerosis and coronary disease. In those in which the asthma came on suddenly between 40 and 50 years of age it was continuous and progressive; in several cases the course was remarkably short and in all death was due to a typical asthmatic paroxysm. The author concludes that in this series the pathology which he believes to be characteristic of death from asthma occurred principally in the older age group; this conclusion, however, is not borne out by the findings in a series of 58 cases which were collected from the literature and are represented in a second chart. In this series the typical pathology was found at necropsy and the ages of the patients show that death because of asthma can occur at any age. The recorded cases in the older age groups were similar in type to those in Rackemann's own chart. The author stresses that such fatal cases are only a small proportion of all patients in whom asthma develops after the age of 45. He considers it reasonable to conclude that in the younger age group the symptoms were mostly due to bronchospasm caused by hypersensitivity to foreign material. When, however, the asthma had persisted over a period of time the factor of bronchial exudate appeared. This is initially thin but is liable at any time to thicken and to obstruct the bronchi so that the patient suffocates.

Clinical picture

Types in childhood

Aetiology studies of asthma in children.—Derbes and Engelhardt state that a review of the literature indicates that bronchial asthma is regarded as a contributory cause in the production of heart disease. Since in adults it is not possible to exclude other concomitant causes, for the purpose of their study the authors examined the cardiac condition of 13 children between the ages of 5 and 14 years who for several years had been sufferers from bronchial asthma. The children were examined physically and by x-ray in order to determine the size of the heart, enlargement being considered pathognomonic of heart disease. In no case did physical examination disclose any sign or symptom of heart disease. A preliminary fluoroscopy was carried out followed by the taking of 2 x-ray photographs of all the children. The measurements recorded were the transverse diameter of the great vessels and the longitudinal and broad diameters of the heart; the fluoroscopic results were recorded. It was

noted that all the measurements were within normal limits. The transverse diameter of the heart was further determined by the use of prediction formulae based on height and weight calculations. There is a very close correlation in the findings from the use of both these formulae. The distribution of the cardiothoracic ratio of Danzer is indicated showing results well within the limits of the accepted formula. The only reliable means to estimate the size of the heart is fluoroscopy carried out by an experienced radiologist, combined with the use of prediction tables. As a result of their study, the authors consider that there is no evidence that uncomplicated bronchial asthma produces heart disease.

Treatment

Treatment of attacks

Nasogenic asthma and breathing exercises—Shields describes the treatment of nasogenic asthma by means of breathing exercises and intranasal zinc ionization. At the first session the physiotherapist should explain the nature of the respiratory disorder and the various phases of the normal movements of the chest. The correct movement of the first phase of inspiration is taught by placing the patient in the semi supine position with the knees slightly flexed. The instructor exerts a firm even pressure with the flat of the hand on the patient's upper abdomen. The patient is asked to breathe in and to raise the teacher's hand. This movement can be effected only by a vigorous descent of the diaphragm with consequent expansion of the base of the lung. Proficiency is attained by repetition of the movement and by the patient practising without aid. The second and third phases are taught by placing the hands over the lower ribs in the mid-axillary line and, subsequently, on the upper part of the chest. The patient inspires, thus displacing the demonstrator's hands. The combined phases are now mastered. Expiration is taught by placing the hand as in the first phase. Exhalation should be through the mouth and as if to dislodge imaginary dust in the far corner of the room. The chest should be allowed to sink gradually. No instruction is complete until the breathing is without conscious effort. In treating nasal oedema zinc ionization may cause a secondary reaction but is to be preferred to local applications of substances such as cocaine.

Penicillin in intrinsic bronchial asthma—Hampton and his colleagues report on the use of penicillin in the treatment of intrinsic bronchial asthma. They selected 9 patients with moderate or severe asthma apparently due to bacterial allergy developing after primary bronchial infection. Five patients received a total of 500 000, 1 patient 800 000 and 1 patient 1 300 000 Oxford units of penicillin given intramuscularly. Later, these and 2 additional patients received 500 000 units of penicillin intratracheally by means of a spray and a curved cannula. Bacteriological studies of sputa and of throat and nasal secretions showed a pre-dominance of non group A β haemolytic streptococci, α and γ streptococci and pneumococci. The incidence of β haemolytic streptococci in the cultures decreased after penicillin therapy. The vital capacity, recorded 30 minutes after epinephrine had been injected subcutaneously, was greater in 5 of the 9 cases after penicillin administration. Signs of subacute or chronic bronchitis were noted when bronchoscopic examination of 6 patients was made, and persisted in 2 patients who were re-examined 2 weeks after treatment with penicillin. One patient showed after treatment a transitory positive skin reaction to a 1 in 100 dilution of freshly dissolved penicillin. Despite the evidences of slight clinical improvement noted in 4 cases, the authors consider that penicillin offers no advantage over other types of therapy in the treatment of intrinsic bronchial asthma.

Use of epinephrine (adrenaline)—With regard to the symptomatic treatment of seasonal hay fever and asthma Prickman and Gelbach say that the first principle is to avoid, by environmental change, contact with offending pollens. If this is not possible a simple home-made air filter incorporating an electric fan can be fitted into the bedroom window-frame. Prolonged exercise in country air, especially on windy days, should be avoided and an oral nasal filter mask can be worn out of doors. Eye drops containing epinephrine (adrenaline) hydrochloride, sodium borate (borax), and boric acid are useful for reducing conjunctival irritation. For asthma, epinephrine sulphate with Seconal Sodium (sodium propyl methylcarbinylbarbiturate) Amytal and Nembutal (pentobarbitone) may be given orally. Preparations containing aminophylline may have some additional value. Propadrine hydrochloride alone or with theophylline racephedrine hydrochloride (racemic epinephrine) and Neosynephrin hydrochloride all have less stimulating effects on the central nervous system than has epinephrine. Delayed absorption of some of these drugs if they are given in the form of coated tablets, may prevent symptoms during the night. For severe and moderate asthma epinephrine is still the most effective drug. It is given in 1 in 100 solution in a nebulizer or 1 in 1 000 hypodermically (5–7 minims). In severe cases it may be necessary to give aminophylline in glucose solution intravenously, or this drug can be given as a rectal suppository. The use of intranasal applications of the vasoconstrictor type should be guarded since the ensuing vasodilatation may aggravate the swelling of the mucosa. If specific measures prove to be unsatisfactory, administration of vitamin C in large doses may be of benefit. A warning is given against the use of morphine and related drugs as cough sedatives in cases of asthma.

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Rackemann, F. M. (1944) *J. Allergy*, 15, 249.

Shields, C. (1944) *Brit. J. phys. Med. N.S.*, 7, 173.

Soysa, E., and Jayawardena, M. D. S. (1945) *Brit. med. J.*, 1, 1.

AVIATION MEDICINE

See also B.E.M.P., Vol. II, p. 239; and Cumulative Supplement, Key No. 116.

Physiology of aviation

Effects of flying on the human being

Altitude and intracranial pressure.—It has been stated by various authorities that intracranial pressure is increased at high altitudes. Peterson, Kent and Cone report the results of a study of the effects of altitudes on the intracranial pressure in a patient with a very large cranial defect caused by a Sten gun bullet. The defect, at the time of the investigation, measured $16 \times 10 \times 2.5$ centimetres, was perfectly healed and freely mobile under artificially increased intracranial pressure. The investigations were carried out in a decompression chamber large enough to accommodate 12 persons. The patient was exceptionally cooperative throughout and emotionally stable. The intracranial pressure was studied at various altitudes up to 30,000 feet and under conditions of sudden and more prolonged anoxia, by means of direct observations on the cranial defect, herniometric recordings with photographic check and a plethysmograph, and by recording the spinal fluid pressure through a lumbar puncture. This last was made possible by completely closing the cranial defect with a freshly poured quick-setting plaster cast, firmly strapped into position. All the experiments showed that no significant increase in the intracranial pressure in man, apart from normal variations, occurs at high altitude and under conditions of sudden or more prolonged anoxia. These results give no contra-indication, based on changes in intracranial pressure, to the transportation of casualties and sick persons by air. Experience with other patients with head injuries has shown that they tolerate air transportation well, and life may be saved by obtaining specialized treatment quickly.

Peterson, Bornstein and Jasper report on the result of an investigation into the effect of altitude on intracranial pressure, undertaken for Canadian Army Medical Research. After a critical survey of animal and human experiments by many investigators reported on in the literature, it was concluded that there was no evidence that reduced atmospheric pressure in itself had any influence on intracranial pressure, but that intracranial pressure may be increased, (1) by the expansion of gas in the bowel at reduced atmospheric pressure, secondary to a rise in venous pressure; (2) as a result of the production of cerebral oedema due to anoxia caused by breathing air at high altitudes; (3) possibly by increased arterial blood pressure due to anoxia. Changes in the rate of production or of absorption of cerebrospinal fluid under conditions of anoxia may compensate for increases in intracranial pressure produced by these three mechanisms. It is recommended that the following factors be studied quantitatively for the proper investigation of intracranial pressure at various altitudes: venous pressure; presence of abdominal distension; oxygen tension in the gas mixture breathed; oxygen saturation of the blood; cerebrospinal fluid pressure; in animal experiments, amount of cerebral oedema due to anoxia; chronicity of anoxia; in human experiments, emotional response and bodily relaxation; in experimental animals, relaxation produced by anaesthesia. According to the experimental evidence in the literature, significant increases in intracranial pressure will not occur in the sick or wounded transported by air provided anoxia is not permitted to occur.

Diseases associated with aviation

Acute otitic barotrauma

Findings during decompression tests.—Dickson, McGibbon, Harvey and Turner describe an investigation into the incidence of acute otitic barotrauma as a disability amongst 1,000 aircrew cadets during a decompression test. Acute otitic barotrauma is caused by differences between the atmospheric and intratympanic pressures during flying and during decompression or recompression in a chamber. The symptoms are pain, with or without deafness, and the tympanic membrane on examination may be invaginated, congested or occasionally haemorrhagic. There may be an effusion into the middle ear, and in severe cases, but rarely, a rupture of the tympanic membrane. Of 1,000 aircrew cadets subjected to decompression at a pressure equivalent to an altitude of 10,000 feet, acute otitic barotrauma developed in 89 and of these only 7 failed in 3 successive tests. The subjects had all been instructed in the technique of middle ear ventilation and without this the authors believe the incidence would have been greater. Analysing possible contributory factors in the occurrence of the syndrome, the authors found that subjects with a previous history of aural complaints were slightly more likely to suffer from this than the rest. Other contributory factors were a history of nasal catarrh, an active cold and objective non-patency of the pharyngotympanic tubes. Abnormalities of the tympanic membrane, obstructive deviations of the nasal septum and malocclusion of the teeth did not appear to be contributory factors. In addition to the 89 cadets suffering from acute otitic barotrauma, 325 showed a varying degree of vascular engorgement of the tympanic membrane with or without minimal symptoms. The authors compared the methods used to ascertain that air entered the middle ear during auto-inflation, and they found that subjective sensations felt during Valsalva's manoeuvre are not a reliable indication that auto-inflation has been successfully achieved. Comparing the visual and auditory method of estimating successful inflation of the ear they found that amongst

those unaffected by barotrauma the visual method was positive in 95.7 per cent of cases and on auscultation only in 52.8 per cent. The authors conclude with recommendations that subjects with previous aural histories should be tested in the decompression chamber before they are accepted for aircrew duties. Scarred tympana or healed perforations are not contributory factors to barotrauma, provided there is sufficient hearing, these conditions should not be a cause for rejection. No aircrew members should fly when they have acute respiratory infections. Subjects suffering from recurring otitic barotrauma with gross malocclusion should be given medical advice and should be supplied with an acrylic bite to be used if there is no improvement in their condition. This treatment should be carried out carefully with radiological control.

Decompression sickness

Experiments with artificial decompression—Decompression sickness is an acute disease with many manifestations produced by exposure to reduced atmospheric pressure. Although recompression effects a cure, several sequelae may occur. Bridge and his associates record the nature and incidence of symptoms, occurring during and after artificial decompression, experienced by a group of volunteers in a chamber in which the decompression was equivalent to that obtaining at 38,000 feet. Conditions thus imitated those met with by aircrews at such an altitude. The men performed in the chamber a 30-second 10-step exercise on to a 9 inch platform and repeated it every 5 minutes until decompression sickness severe enough to cause "descent" developed, or until they had remained at 38,000 feet for 90 minutes. Eighty prematurely in forced descent. The major cause was joint pain, most commonly in a knee. Minor causes were chest symptoms, abdominal gas pain and hyperventilation. Nearly 10 per cent of descents were due to muscle pains and syncopal reactions. Joint pains, with or without descent, occurred in nearly two thirds of all man runs and a knee was the joint most frequently affected particularly in its anterior position. Moderate and severe chest symptoms were associated with joint pain in a statistically significant number of instances. A quarter of those having joint pain at altitude had trouble with the same joints during post flight hours and nearly half the number of lesions were joint swellings, probably representing synovial or burst effusion. Ear symptoms usually occurred the morning after the flight and probably were due to absorption of oxygen accumulated in the middle ear during the flight. Ordinarily the pain or stuffiness was promptly relieved by equalizing the pressure between middle and outer ears.

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Peterson, E. W., Bornstein, M. B., and Jasper, H. H. (1944) *Arch. Neurol. Psychiat.*, Chicago, 52, 400.

— Kent, B. S., and Cone, W. V. (1944) *Arch. Neurol. Psychiat.*, Chicago, 52, 520.

BACKACHE AND LUMBAGO

See also B. E. M. P., Vol. II, p. 251, and Cumulative Supplement, Key No. 117.

Diagnosis

Intrinsic causes

Concealed discs—Dandy expatiates on recurrent attacks of low backache without sciatica and reports on 20 cases. He considers that absence of sciatica does not increase difficulty of diagnosis or localization of the affected disc or discs and emphasizes the presence of more than one abnormal disc in 80 per cent of cases with or without sciatica. He condemns, owing to their various dangers, diagnostic injections and holds that 98 per cent can be successfully diagnosed from symptoms, signs and skiagrams, although spinal tumours, the symptoms and signs of which may exactly simulate those of defective disc, occasion diagnostic difficulties. The author thinks weakness of the lower lumbar spine to be the underlying cause of defective discs, with indirect trauma caused perhaps even by a sneeze, an additional factor. He believes that concealed discs—that is small discs that do not elevate the nerve—constitute three fourths of the total number and that they are as easily localized and treated as are large ones. Dandy stresses the importance of complete removal of affected discs because after partial removal there will be recurrence of symptoms in at least a third of the number of cases—and in any case the protrusion, in concealed discs, is too small for excision. Complete removal achieves rapidly that narrowing and filling with connective tissue of the joint, which nature very slowly attempts to do. Three months after complete excision the was demonstrated 4 years after operation, was found to be absolutely firm in one case bony union fusion operations. Complete excision of discs obviates the need of

Lumbosacral lesions and the radiologist—Brailsford¹ discusses the value of radiology in lumbosacral lesions. The assessment of the clinical data in cases of low backache is difficult. Many cases are of a temporary or recurrent nature and this fact should receive full cognizance when the radiological discovery of an anatomical anomaly is being considered. Radiology

in such cases should not be neglected since previously unsuspected severe lumbosacral lesions may be disclosed. In recurrent cases without initial radiological signs, the author has in some cases after 2-3 years demonstrated lipping of the margins of the vertebrae or articular processes, suggestive of an inflammatory condition. Developmental irregularities are often disclosed in the course of other investigations and are unassociated with symptoms. Brailsford describes some of the pathological conditions which may develop consequent upon the strains and stresses of adult life upon certain anatomical maldevelopments. In many cases of trauma no radiological signs are found. In severe cases, although no initial signs are present, after a period such changes as a localized osteoporosis followed by ossification of the ligamentous insertions may be demonstrated. The possibility that trauma may have aggravated previous disease such as tuberculosis, syphilis or neoplasm must be considered. Lesions of the intervertebral discs may be recognized by plain x-ray films. Protrusions of the disc into the spinal canal require a special examination with the aid of Lipiodol (iodized oil) for the purpose of demonstrating them. Spectacular recoveries have been recorded after their operative removal in cases which showed signs and symptoms of cord pressure. When considering protrusions as a cause of backache and of sciatic pain, however, their anatomical frequency and significance must be fully appreciated. In persons without symptoms protrusions are not uncommon; they are relatively stable and are not subject to the recurrent disturbances and recoveries which are often seen in lumbago and sciatica. Thus Brailsford considers that the patient must be most thoroughly investigated from every angle and that the presence of a hysterical factor must be envisaged before a major surgical procedure is adopted.

X-ray examination.—Brailsford² discusses the value of radiology in the investigation of lumbosacral lesions, one of the many possible causes of low back pain; other causes are maldevelopment, injury, and inflammation or neoplasm of the skeletal, nervous, gastrointestinal, vascular and genito-urinary systems. Severe pain may be felt in the lumbosacral region in the early stages without there being any demonstrable lesion. Radio pictures taken some time later have shown lipping of the margins of the vertebral bodies or articular processes, indicating a previous localized inflammation. Asymmetrical development of the fifth lumbar or the first sacral vertebra, symptomless at first, may produce traumatic arthritis through strains caused by imperfect balance. Spondylolisthesis and other pressure deformities may give rise to pain and disability. In lumbago caused by the lifting of heavy weights no spine lesion is seen by skiagrams. In severe trauma to bones and ligaments reactive changes are seen later, for instance localized osteoporosis and ossification of ligaments. An injury may aggravate dormant disease which may have been symptomless before the trauma, and tuberculous caries, syphilitic gummata, neoplasm and active aneurysm may be overlooked without skilled radiography. Disc lesions may be recognized from the plain radio picture, and protrusions from the disc into the spinal canal may be seen after the injection of Lipiodol (iodized oil). It is relatively common, however, for these to be present without symptoms. They are relatively stable and are not subject to the recurrent disturbances and recovery which are seen in lumbago and sciatica. The disc may be severely damaged by surgical manipulation; degenerative changes develop in it, and reactive changes occur in the approximated surfaces of the vertebral bodies.

Importance of accurate diagnosis prior to treatment.—Turner stresses the importance of accurate diagnosis prior to manipulative treatment of low back pain. He advises careful exclusion of visceral disease, search for local sepsis or toxæmia, detection of abnormal posture and the taking of detailed history concerning occupation and injuries. Hospital or nursing-home facilities are considered to be essential for adequate investigation of chronic backache. The author states that the importance of x-ray examination of spine and pelvis "cannot be over-emphasized" and urges special caution concerning early tuberculous spine and sacro-iliac joint. He considers sepsis and toxæmia to be important, not only in producing chronic backache conditions but also in preventing recovery after manipulation. The straight leg test for sacro-iliac strain in which pain is experienced on lifting the contralateral leg beyond 80°, should be made, because the sacrum is then rotated backwards on the ilium of the affected side; raising the leg of the affected side beyond 70° causes pain in the sacro-iliac joint since movement occurs in the joint. Turner advises manipulation for chronic joint strain in sacro-iliac and lumbosacral joints and for radiculitis which affects the lumbosacral nerve roots which may have become adherent to surrounding structures, especially near the intervertebral foramina. Manipulation should not be carried out in cases of "sciatica" due to congenital deformities, in well defined arthritis of lower lumbar joints, in prolapse of nucleus pulposus, and in tumours or inflammatory lesions within or outside the spinal canal. The author emphasizes the importance, after manipulation, of re-education of muscles, if this is possible, in order to correct faulty posture so that a support may be unnecessary. Application of radiant heat and treatment by deep massage of fibrositic areas immediately after manipulation is recommended.

Brailsford, J. F. (1944)¹ *Brit. J. Radiol.*, 17, 308.

— (1944)² *Med. Pr.*, 212, 315.

Dandy, W. E. (1944) *J. Amer. med. Ass.*, 125, 1175.

Turner, J. M. (1944) *Med. Pr.*, 212, 202.

BITES AND STINGS

See also B.E.M.P., Vol. II, p. 343.

Snake bite**Treatment**

Report on three cases—Earle reports on 3 cases of snake bite which occurred in the coastal region of Northern Peru and were admitted to hospital during 1943. The patients were admitted from one to one and a half hours after being bitten. All showed fang marks with oedema at the site and swelling on the proximal part of the limb. Two ampoules of anti snake venom serum were injected intramuscularly. One patient, 15 hours after the bite, had a sharp haemorrhage from the mucous membrane of the mouth. A second full dose was given, one ampoule being given intravenously. Another patient was given a second dose 4 hours after the first. Each chart showed a rise of temperature after the injection. The patients were discharged from hospital after 3-5 days. The type of snake responsible is the machancha (*Trimeresurus barnetti*), a local small desert pit viper closely resembling the fer de lance (*T. atrox*) but smaller in size. Of other snakes reputed to be poisonous, the commonest is the coral snake distinguished by the arrangement of its black rings in triads. The ignorant among the natives consider all reptiles to be dangerous. Earle describes a non poisonous boa-constrictor, pale in coloration on account of its desert habitat which occurs in that part of Peru.

Earle K. V. (1944) *J. trop. med. (Hyg.)*, 47, 37

BLACKWATER FEVER

See also B. E. M. P., Vol. II, p. 361 and Cumulative Supplement Key No. 135

Treatment**Alkaline treatment**

Criticism of the rationale—Maegraith questions the validity of the hypotheses upon which the alkaline treatment of blackwater fever is based and suggests that the renal failure which occurs is a syndrome which he and Havard describe as tubulo vascular renal, met with in other conditions. The author disputes the theory that mechanical blockage of the urinary tubules explains the failure of urinary flow. Intense haemoglobinuria, he points out, is sometimes present in blackwater fever without oliguria or anuria and in some cases renal failure develops after haemoglobinuria has ceased or may fail to develop after recovery from oliguria although haemoglobinuria persists, some other conditions with excessive haemoglobinuria seldom progress to oliguria and anuria although these may occur in circumstances which exactly parallel the renal failure of blackwater fever without haemoglobinuria. The author has observed that the degree of blockage found *post mortem* is not always consistent with the degree of clinical renal failure. He emphasizes that the urine voided during and immediately after oliguria and anuria is poorly concentrated and often contains neither casts nor debris. Maegraith suggests that the tubulo vascular renal syndrome results from diminished blood supply to the distal convoluted tubules, which causes interference with the function of their epithelium either by anoxia and consequent metabolic changes or by collapse of the vessels into the tubules or vice versa, with resulting reabsorption of urine into the circulation. Although the author grants that alkaline treatment may be of benefit in some cases of blackwater fever by preventing acidosis and by aiding diuresis he emphasizes its reported failure in many cases to alkalinize the urine. He further points out that in any case despite much contradictory evidence, the urine is not necessarily acid in blackwater fever and cites data to show that the sodium chloride concentration does not usually approach the figure at which it would facilitate precipitation of blood pigments. He suggests that in blackwater fever alkaline treatment may even do harm to already damaged kidneys.

Maegraith, B. (1944) *Trans. R. Soc. trop. Med. Hyg.*, 38, 1

BLADDER DISEASES

See also B. E. M. P., Vol. II, p. 374, and Cumulative Supplement Key Nos. 136-146

Neoplasms**Malignant growths**

Transplantation of ureters—Jewett describes a two stage method of uretero intestinal implantation in 33 cases, a modified technique was employed in the last 10 cases and the results were distinctly better. The main difficulties encountered in the second stage in the earlier technique were due largely to adhesions, especially of the sigmoid to the posterior abdominal wall. Gentle handling of the peritoneum with the use of physiological saline at body temperature avoidance of undue traction with good relaxation and complete haemostasis will tend to prevent adhesions. Some fixation of the sigmoid is necessary but not complete fixation as practised in the earlier technique. The lower descending colon is freed from its attachment to the lateral parietal peritoneum allowing of greater mobility of the sigmoid into which both ureters are to be implanted. The right ureter is implanted first. The ureter is exposed by incision through the posterior parietal peritoneum. At a proper level opposite the exposed portion of the exposed ureter is implanted upon the submucosa and is buried by approximation of the seromuscular flaps by interrupted sutures. The incision through which the ureter was lifted is sutured leaving at each end space sufficient to avoid compression of the ureter. The sigmoid with implanted ureter is then rotated laterally in order to present the suture line to the posterior parietal peritoneum and is fixed in this position by several sutures. The second stage is performed 3 or 4 weeks later. The ureter emerging from the

sigmoid bed is often conspicuous with the posterior peritoneum over it. The peritoneum is incised and the ureter is freed downwards and divided between clamps. The sigmoid is then freed from the pelvic wall and the ureteral lumen is calibrated with a bulb sound. The mucosa of the sigmoid is cut through with an electrode having an adjustable cutting wire, thus making an ostium through which the bulb sound is passed to be palpated in the lumen of the sigmoid. The ureteral stump is swabbed with phenol and then with alcohol, is clamped and is securely occluded by 3 ligatures.

Nervous diseases

Treatment

Failure of sympathectomy.—Jacobson, Braasch and Love find that the present conception of a dual innervation of the bladder attributes little importance to the sympathetic nervous system, the main nervous supply coming from the parasympathetic. The sympathetic innervation can be largely dispensed with without causing any significant interference with normal micturition. Hence presacral neurectomy has been performed less and less frequently of late and is only rarely used for the relief of intractable pain in the bladder and for the treatment of neurogenic vesical dysfunction. Sympathectomy has failed to meet the expectations originally held for it, and gradually has been replaced by other operative procedures of proved and established merit such as transurethral resection of the bladder neck. Complete relief in cases of intractable vesical pain is obtained only when the pelvic plexus is removed, and this results in permanent urinary retention and the use of a catheter for the remainder of the patient's life. Out of 37 cases of presacral neurectomy for intractable pain only 3 persons experienced complete relief of pain; in 10 of the others the pain was partially and temporarily relieved. Six of the patients with neurogenic vesical dysfunction out of 25 cases operated on derived some measure of permanent relief, and in 5 of these the relief proved to be only partial. Pathological changes in the tissues of the vesical neck were so extensive in most of these cases that dysectasia and obstruction resulted, which necessitated the taking of local measures. Transurethral prostatic or vesical neck resection was performed in 9 cases with complete relief of symptoms.

Diverticulum

Treatment

Palliative measures.—Harlow discusses the palliative treatment of diverticula of the bladder, which are liable to develop when there is a slowly increasing obstruction to urinary outflow. The occurrence of congenital diverticula depends upon embryology and upon the physiology and pathology of micturition. A congenital weakness or sac may exist at the interureteric bar of muscle marking the line of fusion between the parts originating from the cloaca and Wolffian ducts. The anatomy and physiology of the bladder detrusor muscle, sphincter vesicae, sphincter urethrae and trigonal muscle are discussed. The last mentioned, lying internal to and entirely separate from the detrusor, runs from the ureteric orifices down to and through the internal sphincter and terminates at the verumontanum of the urethra, forming an arc, which on contraction opens wide the vesicle orifice so that the urine escapes into the prostatic urethra and intensifies the reflex contraction of the detrusor muscle. Fibrous infiltration about the vesical orifice interferes with its proper functioning. Typical symptoms are difficult urination, associated with heavily infected urine and, often, with calculi. Infection spreading through the sac wall leads to development of adhesions to surrounding structures. During cystoscopy, the orifices of diverticula appear as black spots. Operative removal is the ideal treatment, before the cause of obstruction is dealt with, but when such removal is too hazardous owing to age and longstanding uropathy palliative methods are indicated. These include instruction in self-catheterization twice daily, combined with postural drainage, routine administration of urinary antiseptics, and postural lavage thrice weekly through the catheter. Carbachol, an acetylcholine derivative which can be given orally, aids the action of the detrusor muscle. Symptoms due to overdosage or allergy can be relieved by administration of atropine. The administration of oestrogen or a Steinach 2 ligature may help in cases secondary to prostatic hypertrophy. Short-wave diathermy applications to the bladder base and prostate aid resolution when fibrous infiltration of the vesical orifice is the cause of a diverticulum.

General

Treatment

Implantation of ureter on skin surface.—Goldstein and Berman introduce a new technique for implantation of the ureter on the skin surface and believe that it is the operation of choice since it involves less risk of wound infection, of sloughing of the ureter and of retraction of the stump. The operative procedure is performed in two stages. A Gibson incision is made with the curve 2 centimetres more medial to the antero-superior spine than is usual. The ureter is isolated 4 centimetres above the bifurcation of the common iliac vessel and freed as far as is possible towards the bladder with sufficient peri-ureteral tissue to ensure blood supply. A loop of ureter is brought up to the anterior abdominal wall and held in place by rubber tubing. A long black silk suture is placed around the peri-ureteral tissue at its farthest point and returned along the ureter to the skin. The muscles and fascia are then sutured with interrupted catgut placed proximal, under and distal to the loop of ureter, and the skin sutured over the ureter. After several days the distal part of the incision is opened up. With the black silk suture acting as a guide, the distal end of the ureter is separated

down towards the bladder where it is doubly ligated, the proximal part is clamped and the ureter bisected. The proximal stump is brought up on to the abdominal wall which is closed around the ureter, in which a ureteral catheter is placed, a small rubber drain having been inserted into the area of the distal stump. A Foley catheter may be inserted into the renal pelvis. The length of the available stump may allow of the fixation of a suitable urinal and avoid the necessity of using a catheter, the stump protruding between 2 and 3 centimetres beyond the anterior abdominal wall.

Goldstein, A. E., and Berman, E. F. (1944) *J. Urol.*, 52, 224

Harlow, F. W. (1945) *Med. Pr.*, 213, 276

Jacobson, C. E., Braasch, W. F., and Love, J. G. (1944) *Surg. Gynec. Obstet.*, 79, 21

Jewett, H. J. (1944) *J. Urol.*, 52, 536

BLASTOMYCOSIS

See also B. E. M. P., Vol. II, p. 403, and Cumulative Supplement, Key Nos. 147 and 148

Coccidioidal granuloma

Clinical picture

Denenholz and Cheney report on 14 cases of proved clinical coccidioidomycosis—10 patients having infections of the primary benign type and 4 of the disseminated type—and on 30 patients for whom the diagnosis had been proposed, owing to a positive cutaneous test, but in whom it was not subsequently confirmed. In making a diagnosis of coccidioidomycosis the importance is stressed of a history of exposure in an area in which the disease is endemic, such areas in the United States of America are the southern half of California, southern Arizona and western Texas. The authors believe that there are no pathognomonic symptoms or physical signs of primary coccidioidomycosis, the manifestations are bizarre and varied, cough, chronic pulmonary disease who has lived in an endemic area the possibility of the disease should always be considered. The disparity between the marked radiological signs and the absence of grave constitutional symptoms is a clinical point of importance in patients with cavitation. The cutaneous test with coccidioidin is of great value, especially when it is positive after a previous reaction known to be negative. A positive reaction probably has the same value as has a positive reaction to a tuberculin test in tuberculosis. The diagnosis may be confirmed by animal inoculation and culture which usually may be readily performed when there are discharging sinuses in a disseminated case, in a primary pulmonary case recovery of the fungus may be technically difficult. Serological tests are of both diagnostic and prognostic importance. Denenholz and Cheney are of opinion that a diagnosis of the disseminated disease should rarely if ever be made in the absence of antibodies of high titre. Radiological appearances may be varied, a characteristic finding is a thin-walled balloon-like cavity. Treatment should be directed to help the patient to localize the infection, and is mainly symptomatic, with complete rest in bed. Immobilization of the lung by the placing of a bag containing lead shot on the anterior aspect of the portion of the chest involved appeared to help some of the thin-walled cavities to close. In the disseminated type the authors consider that immunotransfusion from donors with focalized coccidioidal lesions is a treatment worth trying.

Denenholz, E. J., and Cheney, G. (1944) *Arch. intern. Med.*, 74, 311

BLINDNESS

See also B. E. M. P., Vol. II, p. 407, and Cumulative Supplement, Key Nos. 149–162

Congenital defects

The globe

Cyclopia—Krafka describes 2 cases of cyclopia, the first in a kitten and the second in an infant and presents a new explanation of the occurrence. The kitten had a single massive eye in the midline with a hairy snout overlying the upper margin of the orbit. In the infant the face was normal except for the single central eye, three eyelids and the absence of a nose. The incisive bones were absent, but the maxillary palate was normal. Six types of cyclopia with wide variations of nose and upper lip have been described and many theories have been advanced concerning its cause. Mann based her view on the reduction of the optic angle. Krafka has investigated the state of the first branchial arch at the stage when cyclopia arises which happens early as is shown by Mall's specimen of 6.9 millimetres crown-rump length. An embryo of 3.6 millimetres shows the beginning of the division of the first arch into mandibular and maxillary segments and the author states that angiogenesis is most active at the stage at which the optic rudiments are formed. Normally the two plexuses representing the first aortic arch remain separate in the head region but if fusion should occur a traction factor would result against which the optic rudiments moving from the midline would have to act. Vascular variability is so common that it must occasionally happen here, and this mechanical factor would account for all grades of cyclopia and arhinia. The single eye would be directed towards the head ectoderm at one of 3 levels, (1) below the site of the nasal placodes, (2) at the level of the site or (3) above it, with resultant deformities.

Trauma

Perforating wounds

Removal of foreign bodies—Trevor-Roper discusses the late results of removal of magnetic

intra-ocular foreign bodies in a series of 154 patients treated at Moorfields Eye Hospital, London, during the first four years of the recent war. In 150 cases the anterior route was used. In the remaining 4 cases 2 foreign bodies were removed through the scleral wound and 2 by the posterior route. Removal by the interior route was effected by a hand magnet through a keratome section. In 15 per cent of the cases the foreign body lay in the anterior chamber, in the remainder it was drawn into the anterior chamber by a Haab magnet and was then removed. The final vision was estimated 6–24 months later in all but a few cases. It was found that lens and uveal damage are unfavourable factors in assessing prognosis. The site of entry of the foreign body also affects the prognosis; wounds of the cornea have the best prognosis and wounds of the limbus the worst. Slight delay in removal of the foreign body does not appear seriously to prejudice the prognosis. On analysis of the whole series of 150 cases 30 per cent had final vision of 6/9 or more, 20 per cent 6/12–6/60, and 32 per cent less than 6/60. In 18 per cent the eye had to be excised. Lens damage occurred in two-thirds of the number of cases but sufficient vision was retained in 14 per cent of these to allow of reading. When there was no lens damage 65 per cent retained good vision.

Inflammation

Inflammation of conjunctiva

Ophthalmia neonatorum as a virus infection.—Virus ophthalmia neonatorum is discussed by Sorsby, Hoffa and Young. They review the literature and the history of the discovery of this type of ophthalmia neonatorum and describe a series of 28 cases. At White Oak Hospital, Swanley, Kent, during 1942, out of a total of 269 cases of ophthalmia neonatorum 28 cases (10·4 per cent) of inclusion blennorrhoea were diagnosed. The diagnosis was made by the finding of extranuclear cytoplasmic inclusion bodies in scrapings of the conjunctiva. These were stained by Giemsa's stain. One case was of a boy aged 2 years and could hardly be classified as ophthalmia neonatorum. Of the remainder 24 were bacteriologically negative and the infections in the others were haemolytic streptococci, Koch-Weeks bacillus and scanty diphtheroids and staphylococci respectively. In the majority of the cases the onset was after the sixth day after birth. The corneas were clear in all cases except one and in only 6 cases was the discharge classified as profuse. Apart from one patient treated with penicillin locally, all were treated with oral sulphonamides and the majority showed clinical cure in 4–8 days. No appreciable difference in response could be detected to the various types of sulphonamides. The mothers were admitted with their babies in 25 cases and in 5 cases inclusion bodies were found in scrapings from the cervical epithelium. The authors state that the presence of inclusion bodies does not necessarily prove that these cases of ophthalmia were of virus origin; inoculation experiments would have been necessary in order to prove this. They were, however, morphologically similar to those found by other observers. Sorsby and his colleagues conclude that in this study, apart from a usually later onset, inclusion blennorrhoea was similar in course and in response to sulphonamides to those observed in microbial ophthalmia neonatorum.

Ophthalmia neonatorum and the sulphonamides.—Sorsby and Hoffa¹ discuss the choice of sulphonamide in treating ophthalmia neonatorum. Sulphanilamide was discarded because, although therapeutically effective, it was badly tolerated. Eighty-eight per cent of 133 patients treated with sulphapyridine were clinically cured in 8 days after an initial dose of 0·25 gramme followed by a maintenance dose of 0·125 gramme 4-hourly, day and night, and continued for 2 days after apparent cure. Although there were no serious toxic complications no baby was entirely free from toxic symptoms. Sulphathiazole, sulphadiazine and sulphadimethylpyrimidine were tried and the last named was eventually used for routine treatment, which is: preliminary swabbing for smear preparation and culture; irrigation with half-physiological saline at room temperature; instillation of 1 per cent atropine drops and of drops of liquid paraffin; 0·25 gramme of sulphadimethylpyrimidine, crushed and administered in a teaspoonful of water or milk. Administration is continued in doses of 0·125 gramme 4-hourly, day and night, and until 48 hours after clinical cure. When discharge is profuse, the eyes are irrigated 3-hourly with the saline solution for one day—for longer if necessary. Medicinal paraffin is instilled after irrigation, and atropine is instilled three times daily when corneal haze or ulceration is present. Initial severity of the affection does not appear to influence the response to the treatment. A small proportion of cases appears to be sulphonamide-resistant.

Ophthalmia neonatorum treated with penicillin.—Sorsby and Hoffa² state that the local treatment of ophthalmia neonatorum with penicillin forms a satisfactory alternative to general therapy with sulphonamides. Moreover, the former method avoids the danger of producing sensitization, a risk that is possible if sulphonamides are employed. The report is based on the treatment of 47 infants suffering from the disorder. The concentrations of the solutions of penicillin ranged from 500 to 2,500 Oxford units per cubic centimetre, and the drops were instilled after the eyes had been irrigated with half-physiological saline. The irrigations were omitted as soon as the eyes ceased to discharge. A mild transitory flushing of the conjunctiva was observed in a few cases, but apart from this the drug was well tolerated. An increasing proportion of satisfactory results was obtained with increase in the concentration of the drops used. In only 3 of 8 cases was there cure with the weakest of the preparations but, with the strongest solution, 21 out of 22 infants recovered. Penicillin appeared to be effective against all the common causal organisms of ophthalmia neonatorum. Diphtheroids and inclusion bodies were found to be the most resistant to the drug. Temporary recoveries

were noted in 2 of 3 cases of inclusion blennorrhoea. The time taken to achieve a clinical cure varied from 3 to 100 hours but the rapidity of cure did not always depend upon the severity of the infection. Five cases responded well to penicillin after a poor or protracted response to sulphonamides.

Degenerations and optic atrophy

Degenerations of the macula

Senile macular degeneration—Senile macular degeneration has been recognized as a condition which does not produce total blindness but which is uninfluenced by any form of treatment. Laird restates the opinion of Duke Elder and others that it is due to sclerosis and obliteration of the choriocapillary lamina of the choroid. It is probable that heredity is the major factor in many cases, predisposing as it does to senility and sclerosis. In the early stages examination of the macula usually shows slight disturbance of pigment or paleness with or without sclerosis of the retinal vessels. Later, pigment manifests itself as small light or dark dots. Retinal sclerosis is nearly always present at this stage. Still later, the pigment changes are conspicuous and in the end stages the macula is almost entirely destroyed, only a few clumps of retinal cells remaining. Senile macular degeneration occurs on a series of 67 patients treated with iodides, given orally or subcutaneously. Laird reports that on a series of 67 patients treated with iodides, given orally or subcutaneously. Oral administration was of protiodide of mercury in 0.125–0.25 gramme tablets thrice daily. If intolerance developed Lugol's solution or saturated potassium iodide was substituted. Treatment was continued as long as the vision improved and then was given on alternate months for the purpose of preventing recurrence. An iodide preparation given subcutaneously occasionally produced improvement when oral methods failed. Of 115 eyes under treatment, the average visual improvement was 89 per cent. The maximum noted was 22 times the original vision. The mode of action of iodides in relation to the condition is not known. In animal experiments iodides have been shown to produce vasodilatation and a fall of blood pressure, providing an active thyroid gland is present, to prevent the occurrence of atheromatous vascular changes in rabbits fed with cholesterol.

Vascular and blood diseases

Haemorrhage

Further aetiological considerations—Amblyopia resulting from haemorrhage is described by Cox. After profuse distant haemorrhage—most commonly gastric, but sometimes uterine, intentional, nasal, traumatic or pulmonary—a sudden diminution of vision occasionally occurs which frequently progresses to complete and permanent blindness with atrophy of the optic nerve. Many theories of the pathogenesis of this condition have been given from the earliest of haemorrhage into the optic nerve sheaths, to the latest that the blindness is due to a vasoconstrictor toxin, probably epinephrine (adrenaline). The blindness, usually bilateral, may be transitory or permanent and usually occurs between the third and the seventh days after the haemorrhage but it may be delayed. A case is reported of a soldier who had severe internal haemorrhage after his chest had been crushed in an accident. Three days later his vision was limited to telling the difference between light and darkness only. Both fundi were ischaemic. Vision cleared very slowly, 18 months later both discs showed incomplete atrophy—the pallor involving the temporal side—the arteries were constricted and the veins were full. There was an absolute central scotoma in both eyes with concentric areas of clear peripheral vision. Experiments on dogs and rabbits showed that blindness after massive distant haemorrhage was due to degeneration of the ganglion cells of the retina and their long processes which make up the centripetal fibres of the optic nerve. The amount of blood lost does not affect prognosis. Improvement is always slow and is possible even after loss of perception of light provided pupillary reaction to light is retained.

General

Treatment

Principles of prosthetic treatment—Brown describes prosthetic principles when the entire orbital contents are removed. The skin should be soundly healed. In order to avoid sagging due to the erect posture, the orbit should be sculptured slightly higher on the face than its opposite and more of the conjunctiva should be made visible. A negative impression is made of the normal side in plaster with the eye closed or in gelatinous compound with the eye open. Modern compounds require to be mixed with distilled water only since they react chemically to form a highly elastic gelatinous mass. The eye is anaesthetized and the mixture is applied for 3 or 4 minutes. It is then removed and fixed in a hardening solution. An hour after the mass has become set a positive cast can be made and the positive separated from the negative in another hour's time. After the stone becomes hard the positive cast is suitably sculptured and the position of the eye is determined, the upper lid being made slightly thicker to enable it to take the roots of artificial eyelashes. A two-piece mould made with freshly mixed plaster contains the sculptured restoration. The two parts of the mould are separated, the sculpture is removed and the clay is washed out. A channel is made through the posterior part of the mould through which the rubber solution is introduced. It is advisable to keep a record of the latex compound used and of the formula for each prosthesis. The art of the prosthetist consists not in making a beautiful organ but in rendering the absence of the organ as inconspicuous as possible.

- Brown, A. M. (1944) *Arch. Ophthalm., N.Y.*, **32**, 208.
 Cox, R. A. (1944) *Arch. Ophthalm., N.Y.*, **32**, 378.
 Krafka, J., Jun. (1945) *Arch. Ophthalm., N.Y.*, **33**, 128.
 Laird, R. G. (1945) *Amer. J. Ophthalm.*, **28**, 287.
 Sorsby, A., and Hoffa, Elizabeth E. (1945)¹ *Brit. J. Ophthalm.*, **29**, 141.
 — — (1945)² *Brit. med. J.*, **1**, 114.
 — — and Young, Elizabeth N. (1944) *Brit. J. Ophthalm.*, **28**, 451.
 Trevor-Roper, P. D. (1944) *Brit. J. Ophthalm.*, **28**, 361.

BLOOD EXAMINATION

See also B.E.M.P., Vol. II, p. 457; and Cumulative Supplement, Key Nos. 163–169.

Serological tests

Haemagglutination (blood grouping)

The Rh factor.—Pieri and Schwartz maintain that every doctor who performs blood transfusions or who has under his care expectant mothers or newborn babies should have a thorough knowledge of the blood groups and of iso-immunization. The authors describe, with illustrations, the blood groups O, A, B and AB and their relationship to each other. The antigens M, N, MN and P, without corresponding iso-agglutinins in human sera, do not produce human transfusion reactions; they do however produce hetero-agglutinins when injected into animals. Rabbit serum, containing agglutinins produced by the injection of blood cells from the *Macacus rhesus* monkey, clumps not only the erythrocytes of the monkey but those of 85 per cent of human beings, regardless of their blood group. The remaining 15 per cent of human beings have none of the *Macacus rhesus* agglutinin and are termed Rh negative. The transfusion of Rh positive blood into Rh negative individuals causes development in the latter of Rh positive agglutinins which, on a subsequent transfusion of Rh positive blood, cause agglutination of the donor's cells. The reaction may cause death, and its prevention lies in the employment in these cases of blood from an Rh negative donor of appropriate grouping who has not been previously immunized. Most cases of erythroblastosis fetalis show hydrops, jaundice or anaemia accompanied by evidence of blood regeneration. About 90 per cent of these infants inherit the Rh factor from the father, transmitted as a Mendelian dominant character. The Rh positive cells of the baby stimulate the mother's blood, which is Rh negative, to produce specific anti-Rh positive agglutinin; this filters through the walls of the villi into the infant's circulation *in utero* and produces blood destruction. The initial passage of the baby's Rh positive cells into the mother's circulation occurs, in the authors' opinion, from injury of the extremely delicate placental villi. Any expectant mother with a history of reaction to a previous blood transfusion or unexplained abortion, miscarriage or stillbirth, should be regarded with suspicion, and so should the occurrence in labour of bile-stained amniotic fluid. In treatment, the oxygen tent and immediate transfusion to the baby of Rh negative blood are called for.

Determination of Rh group in antenatal clinics.—An investigation was undertaken by Murray into the value of a routine determination of the Rh group in antenatal clinics, and in the hope of shedding further light on difficult problems of Rh estimation. The blood of every pregnant woman attending the clinic was tested with several well-tried human immune sera for Rh reaction and those found to be Rh negative were tested for antibodies. In about the first 90 patients the bloods giving negative readings with 3 sera were considered to be Rh negative. In the second 100, 4 sera were used, and the serum of Rh positive mothers was also examined for antibodies, since it was possible that in these mothers antibodies might be developed, or that the factors AB, MN or P might provide the antigenic stimulus. The results of ABO grouping of the 200 cases were: group O, 73 cases; group A, 89 cases; group B, 30 cases; group AB, 8 cases. No examination was made for subgroups A₁ and A₂. The cells were named according to the number of the serum or sera with which they reacted; for example, those which reacted with serum No. 2 were called Rh₂. Twenty-five cases were Rh₂ (or negative), and of these the sera of 2 contained Rh antibodies, one of which was a 70 per cent (or No. 1) serum from a woman who had had transfusion from her husband after a previous postpartum haemorrhage, and the other was an 84 per cent (or No. 3) serum. Although no Rh antibodies were detected in the Rh positive patients of this series, the sera of 4 subsequent Rh positive mothers were found to contain Rh antibodies.

Flocculation and precipitin tests

False positives in Kahn test in respiratory disease.—Zuger and Moffat report the occurrence of false positive Kahn tests in the sera of three brothers aged 11, 10 and 8 years. No treatment was given but the standard Kahn tests became negative 3 weeks later and the more sensitive presumptive Kahn tests were completely negative within 2 months. The father was dead, but the mother's blood yielded a negative reaction. The children were at a camp one month prior to the first examination, and during their stay they had an afebrile upper respiratory infection which did not interfere with their activities. Blood examinations of 8 other children who had stayed at the camp yielded positive presumptive Kahn reactions in 3 instances. Apparently, the changes in the blood were not due to syphilis but were caused by the respiratory infection. The simultaneous and rapid loss of specific flocculating strength of the sera suggests a common and recent antigenic cause. The investigation demonstrates the importance of a period of observation in the case of a family group in which the sero-

logical reactions are suspected to be falsely positive. Such reactions are of special significance in view of the widespread extension of routine testing for the purpose of detecting unsuspected syphilis.

Physical and chemical changes

Sedimentation of red cells

Standardization of haematocrit readings—A method of standardization of haematocrit readings is described by Adams. The haematocrit readily produces sedimentation of erythrocytes, the resulting packed cell volume, expressed as a percentage of the whole blood, being called the haematocrit value. The value can vary with changes in the blood or the haematocrit apparatus. In the first place, the anticoagulant in the sample may be a source of considerable error by altering the osmotic pressure of the fluid around the cells, the author describes an experiment which demonstrates the relationship between varying concentrations of potassium oxalate and packed cell volume, and gives a method of calculating the corrected haematocrit value. Circulatory stasis of 5-9 minutes during collection of the sample causes an average rise of 2.3 points in the haematocrit value. Errors due to variation in temperature are negligible. If allowed to stand at room temperature, the haematocrit value of blood falls during the first 5 hours and then rises above its original value. Variations in the centrifugal force and duration of spinning have a considerable effect on the haematocrit value, and Adams gives a formula by which these can be correlated. Varying lengths of time are needed to obtain a constant packed cell volume at different speeds, the time depends largely on the centrifugal force used, although at high speeds the volume is always lower in spite of a time correction. Blood with great viscosity as in polycythaemia needs a greater centrifugal force than the normal for sedimentation and the converse is true for blood of low viscosity. If all these adjustments are made standard haematocrit values should be obtained.

Adams D J M (1944) *Med J Aust*, 2, 636

Murray, J (1944) *Lancet*, 2, 594

Pieri, R J., and Schwartz, R C (1944) *Surg Gynec Obstet*, 79, 490

Zuger, B., and Moffat, G B (1944) *Vener Dis Inform*, 25, 271

BLOOD PRESSURE, HIGH AND LOW

See also B E M P, Vol II, p 503, and Cumulative Supplement, Key Nos 170 and 171

High blood pressure

Essential hypertension

Treatment by potassium thiocyanate—Koffler, Freireich and Silverman state that it is not certain how potassium thiocyanate acts in reducing the blood pressure in cases of essential hypertension. No therapeutic effect can be assessed without adequate determinations of the amount of the drug in the blood. A study of the unfavourable reports on the use of the drug shows that the toxic manifestations and fatalities were most probably caused by excessive dosage. These unfortunate sequelae might have been averted by a determination of the blood level because the intake is no indication of the amount of thiocyanate available in the circulating blood. Moreover, in order to produce the full therapeutic effect in a series of patients the dosage may vary considerably. Thirty nine patients with essential hypertension were treated for a period of 3 years. There were 17 males and 22 females, the ages ranging from 34 to 71 years. A dosage of 0.1 gramme of potassium thiocyanate given 3 times a day resulted in an average blood level of 5 milligrams per 100 cubic centimetres. In some cases, however, the level was as high as 15 milligrams per 100 cubic centimetres. The blood pressure was reduced in about 50 per cent of cases and there were not any fatalities or severe toxic reactions. A few patients reported subjective improvement in spite of the fact that the blood pressure was not decreased. The patients attended the clinic every week and blood thiocyanate determinations were made at regular intervals. In this way early toxic symptoms and abnormally high blood levels could be detected before dangerous symptoms supervened. The blood concentration remained fairly constant throughout the day, irrespective of the time at which the medicine was taken. There was no correlation between the urinary output of thiocyanate and the daily intake or the blood concentration.

Splanchnicectomy and its results—Smithwick analyses the results of splanchnicectomy on 156 patients, 92 women and 64 men, who were kept under subsequent observation for 1-5 years. In order to denervate the visceral vascular bed an extensive operation with trans-diaphragmatic approach was necessary. The results were classified in 5 groups according to the effects produced on the horizontal resting diastolic blood pressure, the first group showing a lowering of 30 millimetres or more and the fifth group showing a raising of the pressure by a case average of 11 millimetres. A painstaking routine was followed so as to arrive at the horizontal resting diastolic blood pressure and readings were taken in the sitting and standing positions and also of the effects of stimulation by cold. All these readings were made both before and after operation. The results were not all equally good and it is important to determine the circumstances in which the best results may be expected. Patients were tested in their responses to sedative treatment and were graded according to their ocular signs. Three types of hypertension are differentiated according to the width of the pulse pressure. Type (1) has a pulse pressure less than half the diastolic pressure, type (2) a pressure equal to or up to 19 millimetres more than half the diastolic pressure, and type (3) a pulse pressure 20 millimetres or more greater than half the diastolic pressure. Operation results vary with the type, they are best in type (1) and worst in type (3). Subdivisions were made according

to type and sex. These subdivisions will be of greater value when larger numbers of patients have been treated. At operation renal tissue was obtained for biopsy and permitted a further grading of the patients, the majority of whom showed evidence of arteriolar damage. The best results were obtained in women of type (1) and the poorest in men of type (3).

Effect of removal of atrophic kidney.—Mosenthal cites a case in which, as compensatory mechanisms* became strained, a unilateral renal lesion ultimately produced intermittent periods, and then a continuous state, of hypertension. The patient, a woman aged 31 years, when first seen in 1935, had one atrophic functionless kidney due to the compression of the ureteropelvic junction by an aberrant vessel. The average blood pressure for 4 years was 155/95 millimetres of mercury. It then rose to 190/117, returning after a few weeks to its previous level. A year later it rose to 191/111. Nephrectomy was then carried out and the blood pressure fell to almost normal levels, at which it has remained ever since.

Other forms of hypertension

Experiments with intravenous injections of bacteria in dogs.—Dick records the effects experimentally produced in young dogs of repeated intravenous injections of bacteria in amounts insufficient to produce clinical evidence of infection. He seeks to show that one result produced is hypertension. The various organisms, chiefly streptococcal, were obtained from patients with bacterial invasion. Before injections were begun, the normal blood pressure of each dog was ascertained over a period of time. Injections of 50–100 cubic centimetres of a 24-hour broth culture were given on 5 days a week. In one dog thus injected with haemolytic streptococci hypertension developed in 3 months and it died of uraemia, with typical arteriosclerotic appearances of contracted kidney, 5½ years after the first injection. In a dog injected with *Streptococcus viridans* hypertension developed after 4 months, and one kidney excised after 15 months showed slight but distinct increase of connective tissue in the renal blood vessels and glomerular capsules. The blood pressure of a dog which was injected with the green-producing streptococcus (a type of *Strep. viridans*) from urine, rose from 110 to 160 in 20 months, the dog dying after 28 months with infarctions in both kidneys. Injections of colon bacilli were given to 2 dogs. In one the blood pressure rose from 120 to 160 in 1 month, reaching 184 in 11 months. That of the other dog rose from 120 to 140 in 1 month and in 12 months to 150, the dog dying after 20 months. Injections of cultures made from throat haemolytic streptococci, from uncomplicated scarlet fever and from erysipelas all caused a rise of blood pressure. In a number of dogs spontaneous hypertension developed. Some of the injections caused death of the animals before hypertension had time to develop, particularly organisms from subacute bacterial endocarditis. Sterile broth injections in large quantities, identical in composition with those used in the cultures, did not themselves raise the blood pressure.

High blood pressure in general

Treatment

Tests on dogs.—Grimson, Kernodle and Hill describe the results of a study of the effect of activity, rest, sedatives and anaesthesia on experimental neurogenic hypertension in dogs. For part of the experiments they used small sterile buried iliac and femoral cuffs, and pressure sacs connected by fine plastic tubing to a pressure mercury and a recording water manometer. Neurogenic hypertension was developed by excision of the carotid sinuses and division of the vago-depressor-sympathetic trunk of one side and the depressor nerve of the opposite side. In normal dogs the blood pressure was higher in activity than it was during rest and sleep, but in the neurogenic hypertension animals the variations were greater, much higher pressures being recorded during activity although during sleep and rest the pressure did not fall as low as it did in normal dogs. Sodium Amytal and chloralose anaesthesia effected little change in blood pressure of the treated dogs, but deep anaesthesia under Pentothal sodium (soluble thiopentone) and ether produced a drop to the same level as did natural sleep in these animals. Pentothal sodium caused no significant variation in the blood pressure of renal hypertension dogs. The clinical value of these findings is difficult to assess. Clinical neurogenic hypertension, that is hypertension caused by reflex or emotional stimuli, is only one of the causes of increased peripheral resistance which is known to effect clinical hypertension. Rest and sodium Amytal tests which were made on 20 patients treated by paravertebral sympathectomy failed to provide data on which certain benefit by operation could be predicted for any patient.

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Grimson, K. S., Kernodle, C. E., Jun., and Hill, H. C. (1944) *J. Amer. med. Ass.*, 126, 218.

Koffler, A., Freireich, A. W., and Silverman, I. J. (1944) *Amer. Heart J.*, 28, 411.

Mosenthal, H. O. (1944) *Amer. J. med. Sci.*, 208, 210.

Smithwick, R. H. (1944) *Arch. Surg., Chicago*, 49, 180.

BLOOD TRANSFUSION

See also B.E.M.P., Vol. II, p. 530; and Cumulative Supplement, Key No. 172.

Technique of transfusion

Apparatus and procedure

Closed method of preparing plasma.—Walder and Gradis describe a closed method for collecting, centrifuging and pooling blood plasma. They have devised a fireproof glass container of 300 cubic centimetres' capacity, the bottom of which is rounded and constricted

to an internal diameter of 3 millimetres, the constricted part leads to a small bulb of 2 cubic centimetres' capacity and then to a second similar bulb with a hole for passage of a needle, the hole being sealed by rubber tubing. The container is closed by a vaccine cap through which pass an air vent and a needle connected by rubber tubing to the intravenous needle. The whole is assembled, wrapped up and sterilized. By means of a syringe 45 cubic centimetres of 2.5 per cent sterile sodium citrate solution are instilled into the container which is then filled with blood from the vein. The needle and air vent are removed and a rubber cap is drawn over the neck of the container, the rubber tubing over the hole in the bulb being reinforced by a C clamp. The container is placed in a Trunnion cup and centrifuged. It is then placed in a ring stand and the packed cells are drawn off through the hole by a needle, an air vent having been inserted through the vaccine cap. Centrifuging is repeated for the purpose of separating the adherent blood cells and this time the container is inverted on the ring stand, an air vent is inserted and the plasma is drawn off into a pooling bottle, the packed cells being trapped in the two small bulbs. Withdrawn packed cells, when diluted with physiological saline, may be used in blood transfusion for anaemic patients. A clearer and more abundant plasma can be obtained by this method, which allows of pooling on the same day. There is no appreciable disintegration of blood cells and no apparatus with a vacuum is required.

Infusion of blood and other fluids into tibial marrow—Arbeiter and Greengard describe infusions into the tibial bone marrow spaces of infants. The use of the intravenous route is not always an easy procedure in infancy. The bone marrow needle set consists of an outer needle with stylet and an inner hollow drill with an oversize stylet. The leg is immobilized on a back splint. Under local anaesthesia the outer needle is inserted beneath the periosteum just below the tibial tuberosity at an angle of 70–80 degrees to the tibia, with the bevel down and the point distally, in order to avoid the epiphyseal plate. The stylet is removed and the hollow drill with stylet is inserted. The head of the drill is manipulated with downward pressure until a sudden release of resistance shows that the medullary cavity has been reached. Slight pressure is continued until the neck of the drill is within the head of the outer needle, which is then pushed downwards until the whole neck of the drill is again visible. The drill is removed, a syringe full of saline is attached to the needle and aspiration is attempted. If the procedure is correct bone marrow will be obtained. The needle is cleared by injection of a little saline and the infusion must be started rapidly or bone marrow will clot in the needle. All air should be out of the infusion system. In a series of 34 patients, 41 infusions were attempted with 81 per cent completely successful. The patients were all under 1 year old, with one exception. The youngest was 2 days and the oldest 3 years old. Causes of failure were syphilitic osteochondritis and obesity obliterating landmarks. There was partial failure in the 3-year-old, saline ran in well, but blood only very slowly. This suggests that diluted blood might be better for tibial infusions. Fluids used included saline, dextrose, sulpho-amides, diphtheria, pneumococcus and influenzal bacillus antisera, plasma and blood. The average rate of flow per minute in aqueous solutions was 2.3, in plasma 1.4, in blood 0.88 cubic centimetres. Fluids may be injected more rapidly with a syringe, but this may be painful. Contra indications are cases of osteomyelitis and pyogenic septicaemias. X-ray studies showed in one case periosteal elevation and subperiosteal bone formation on the thirty-third day. Otherwise no ill effects were noted. Many of the patients were under sulpho-amide treatment at the time.

Dirty syringes and the blood donor—Mendelssohn and Witts draw attention to the danger of transmitting infection during the withdrawal of blood from a vein in those cases in which only the needles and not the syringe are sterilized for each separate venepuncture. To obtain a venous blood sample it is usual to distend the vein by tourniquet, to insert a sterile needle into the vein in the direction of the heart and to draw up the required amount into the syringe. At this point the hydrostatic pressure in vein and syringe is equal. As the tourniquet must be released before withdrawal of the needle in order to avoid formation of a haematoma, blood then flows through the vein in the direction of the needle point, creating a negative dynamic pressure which, as it increases, will draw blood from the syringe to the vein, thus introducing contamination in the form of infecting virus from a previous case. In this way epidemics of acute hepatitis have originated. Syringes cannot be sterilized merely by rinsing them with sterile water between cases. They must be sterilized by heat. A separate sterilized syringe, as well as needle, should be used in every case of venepuncture whether for intravenous therapy or for the collection of blood samples.

Methods
Wartime advances—Whitby considers the effects on peacetime work of the advances made in wartime of our knowledge of blood transfusion. It was used only to a limited extent towards the end of the war of 1914–1918. The subject has now become a specialized one, requiring highly trained transfusion officers who will be essential for any national medical service in the future. Two fundamental principles must be observed, (1) scrupulous technique in blood collection and (2) immediate refrigeration in order to minimize and delay changes that occur in stored blood. Stored blood is the ideal fluid for both oxygen-carrying and volume-restoring power but carries some danger when the volume to be transfused is large and the blood is somewhat old. In stored blood, leucocytes survive only for a few hours, platelets disintegrate and other changes take place. Research has been devoted to the per-

fection of blood substitutes. None of them possesses oxygen-carrying power. The most widely used is human plasma of which stocks can be built up at leisure for use in any emergency such as road accidents, postpartum haemorrhage and burns. A possible future development is the widespread use of purified human albumin solution, which has already been used by the American Forces. A by-product could also be used as a powerful anti-measles prophylactic. Protein nutrition in addition to carbohydrate infusion is being studied for the purpose of improving the pre-operative condition of bad surgical risks. War experience proved that blood grouping is by no means simple. There are intragroup rhesus factors which influence the outlook on multiple transfusions in pregnancy and on the giving of transfusions to any woman who has been pregnant. These observations have led to measures for the prophylaxis and treatment of erythroblastosis fetalis.

Reactions after transfusion

Reaction due to incompatibility

Acquired sensitivity to the Rh factor.—Young and Kariher report haemolytic reactions due to acquired sensitivity to the Rh factor. The manifestation of sensitivity occurred in women with Rh negative blood many years after immunization by pregnancy. The reactions were encountered in spite of the fact that cross matching by the test-tube centrifuge method had detected no incompatibility. In many cases, apparently, the acquired Rh antibody is not demonstrable by tests *in vitro*. One patient, a woman aged 40 years, was given a transfusion of Rh positive blood. Fifteen minutes after the transfusion was completed she had a mild rigor, but at no time did the temperature rise above 100° F. The urine was dark amber in colour and reduced in quantity. A haemolytic reaction was suspected when the blood non-protein nitrogen was found to be 160 milligrams per 100 cubic centimetres. The reaction was correlated with the fact that the patient about 8 years previously had given birth to a child with haemolytic disease. In another case there was an interval of 16 years between the birth of a child with haemolytic disease and the occurrence of the transfusion reaction. The symptoms consisted of pyrexia, oliguria, jaundice and an increase in the amount of blood non-protein nitrogen. In a third patient jaundice and pyrexia developed after transfusions of Rh positive blood had been given. The woman had never given birth to a child with manifestations of haemolytic disease. There was a past history, however, of chills and fever occurring after transfusions with Rh positive blood. It appears that acquired sensitivity to the Rh factor may persist for many years, probably for life. The haemolytic reactions can be prevented by giving only Rh negative blood to all Rh negative individuals. This necessitates a complete reorganization of the blood bank so that Rh negative blood will always be available.

Effect of transfusion of Rh positive blood into an Rh negative woman.—Drummond, Taylor and Edwards report on iso-immunization to the Rh factor after repeated blood transfusions. The patient, a woman aged 47 years, had never had a blood transfusion and had never been pregnant; she was believed to be suffering from thrombocytopenic purpura, and blood transfusions were given for the purpose of raising the haemoglobin level. The first 3 transfusions were given on the first, second and sixth days, respectively. Five of the 6 donors used were Rh positive, but the Rh group of the sixth donor was not known. During the course of the third transfusion the patient had a rigor and her temperature rose to 103° F., a reaction which was possibly haemolytic in nature. A specimen of the recipient's blood collected on the ninth day was tested for the Rh factor, and the cells gave a good positive reaction. The Rh positive diagnosis induced a false sense of security. Most of the subsequent transfusions were uneventful. It is likely that absence of alarming symptoms was due to the fact that the transfusions were given at very slow drip rates. Further tests showed that the recipient was in fact Rh negative and that her serum contained a potent anti-Rh agglutinin. The original Rh positive diagnosis must have been due to the large numbers of surviving cells of the Rh positive donors in the recipient's blood. Cross matching by the tube-centrifuge technique probably explains why incompatibility was not detected earlier. The tests should be made in tubes by a reliable method.

Indications for transfusion

Surgical cases

Blood lost during surgical operations.—Coller, Crook and Iob describe the estimation and treatment of blood lost during surgical operations. They think that hitherto the ratio between amount of blood lost and total blood volume has been insufficiently emphasized, pointing out the vital difference between the effects of the loss of any given quantity of blood by a very heavy and a very light patient. Carefully recorded blood losses at 626 operations were, in nearly every case, much greater than the surgeons had anticipated. As routine determination of actual blood lost during operation is obviously impracticable, the authors advocate reliance on knowledge of average losses at different operations and present most interesting data compiled from the literature. Average blood loss was greatest (1,084 cubic centimetres) in a group of 30 brain operations amongst which the greatest individual loss was 2,150 cubic centimetres. The greatest individual loss (2,895 cubic centimetres) occurred in the thoracic operation group in which, however, the average loss was 755 cubic centimetres, which was less than the radical mastectomies with an average loss of 732 cubic centimetres and a maximum of 1,272 cubic centimetres. The next greatest average (626 cubic centimetres) occurred amongst the spinal cord operations with a maximum loss of 1,264 cubic centimetres.

Gastric operations had an average loss of 233 cubic centimetres. Biliary tract operations of which, in the series of 626, there were only 16, showed maximum and average losses of respectively 400 and 100, contrasting with an average loss of 594 cubic centimetres in the group of 8 cases presenting difficult biliary tract surgical problems, separately described by the authors, in this group many of the patients had been previously operated on, the majority were jaundiced, in all the common duct was explored or reconstructed, and all the operations were lengthy. Estimation of haematocrit changes, haemoglobin and plasma protein concentration was not found to be of assistance in estimating need for blood transfusions, which the authors advocate should be given during operations involving dangerous loss of blood.

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BONE DISEASES

See also B E M P, Vol II, p 553, and Cumulative Supplement, Key Nos 175-184

Congenital bone dystrophies, generalized

Idiopathic fragilitas ossium

Identical basis of osteogenesis imperfecta and osteopsathyrosis—Rosenbaum considers that osteogenesis imperfecta and osteopsathyrosis are different manifestations of a single disease. This view is strengthened by the case histories of 2 infants with the signs of osteogenesis imperfecta. In all probability both patients had suffered intra-uterine fractures although there was a history of postnatal fractures in 3 members of the family. Chemical analysis of the blood in a patient with osteopsathyrosis showed fluctuations in the values of serum calcium and inorganic phosphorus at various stages of the illness. Therefore, contrary to Glanzmann's opinion, these tests fail to form a basis for distinguishing between the two types of congenital fragilitas ossium. One patient, with a past history of typhoidal meningo-encephalitis, was found to have osteopsathyrosis. It is presumed that the abnormality of the bones developed in response to the cerebral disorder. Signs of increased intracranial pressure were indicated by x-ray of the skull which revealed thin cranial plates and distinct increase in the digital markings. It is believed that this case affords the first instance of osteopsathyrosis with osteosclerotic proliferation of the margins of the vertebral bones. Zondek and Lichtwitz point out that osteoporosis and osteosclerosis may be associated with cerebral disease. The site of the disorder is placed in the infundibular region or in the hypophysis. The author assumes that a similar disorder is the origin of fragilitas ossium and treats cases of osteopsathyrosis with extracts of the anterior lobe of the pituitary gland. The results are encouraging since with this treatment most patients show no additional fractures.

Polyostotic fibrous dysplasia (Albright's syndrome)

Multiple pathological fractures—Albright's syndrome is characterized by bone lesions which are predominantly unilateral and show osteitis fibrosa by brown non elevated pigmented areas of skin usually on the same side as the bone lesions, and by an endocrine dysfunction which in females only is associated with precocious puberty. Multiple pathological fractures may occur, as in the case now recorded by Behrend. The patient, a 7-year-old girl, sustained 3 fractures of the right femur in 2 years, all of which healed successfully. She first menstruated at 3 years of age and again at 7 and at 8 years. Enlargement of the breasts was evident in the eighth year. Small pigmented naevi were present, chiefly on the back, but there was no orderly distribution. The fractures occurred in a cystic area in the right femur and radiographic examination showed similar cystic involvements in the left tibia and in the fibula, tibia, ischium, ilium, humerus, first metatarsal and third and fourth metacarpal bones on the right side. The skull bones were normal. Curettings from the bone cyst in the femur showed multinucleated tumour giant cells and fusiform connective tissue cells, arranged for the most part in bundles. The aetiology of Albright's syndrome is obscure and there is no specific therapy. On the basis of a suggestion first made by Helfet, aluminium acetate was given in this case on the assumption that aluminium acetate ions combine readily with phosphorus for excretion and serve to hoard calcium ions. The conception of calcium and phosphorus metabolism is at variance with generally accepted ideas. Behrend states that, at least, the aluminium acetate did no harm. Additional cystic areas appeared in bones but no enlargement of existing cysts occurred under treatment. The author condemns the exploration of parathyroid glands, previously carried out in other cases, on the grounds that there is no hypercalcaemia in the condition and no evidence of parathyroid tumours.

Chronic osteomyelitis

Treatment

Uses of penicillin—Anderson, Howard and Rammekamp report encouragingly on the use of penicillin in 40 cases of chronic osteomyelitis, of which 25 were observed for a year or longer after treatment. One patient was moribund when treatment commenced. No significant improvement occurred in 5 cases, there was failure in 4 because the infecting organisms became penicillin fast. Two patients clearly improved, although their sinuses never com-

pletely healed. One of these later showed evidence of resorption of visceral amyloid deposits. In 32 patients infection was quickly arrested, but 15 relapsed, in 9 of whom demonstrable sequestra had not been removed. Of 17 patients who remained well, 10 had no sequestra, 6 had sequestra removed at the time of penicillin administration. Nine patients received a second course of penicillin. Including both courses of penicillin therapy, operation was performed in 14 cases. Comparison of the results in this group with those in 26 cases treated with penicillin alone, indicates that infection more probably will be arrested if adequate surgery, when necessary, is combined with penicillin administration. Primary suture after sequestrectomy or evacuation of a bone abscess proved to be very satisfactory in patients who received penicillin parenterally and by local instillation of concentrated solutions through rubber catheters implanted within the bone cavities. Dosage was subject to control afforded by the response of lesions and the results of cultures. At the time of writing, 28 patients had no draining sinuses or other symptoms or signs of active infection.

Tumours of bone

Malignant

Osteogenic sarcoma and dangers of biopsy.—Brailsford² opens his paper on the dangers of biopsy in sclerosing osteogenic sarcomata by quoting Ewing as saying that "the whole clinical and radiological picture of the case of bone sarcoma usually furnishes a better conception of the diagnostic and therapeutic problem than can be obtained from a biopsy", and that "few surgeons realise the limitation in the historical diagnosis of bone tumours and the conditions which simulate or accompany them". Brailsford then describes the histories and progress of 3 patients the first of whom, a woman aged 25 years, reported at the Royal Cripples Hospital, Birmingham, with pain in a knee joint injured by a fall a year previously. Radiographic appearances suggested sarcoma, but the histological report by an expert said: "The cellular structure suggests a chronic inflammatory condition rather than sarcoma." Approximately a year later the patient was readmitted and sarcoma was then diagnosed and x-ray treatment was instituted. The patient died 9 months later. In the second case, that of a woman aged 18 years, the biopsy report stated that there was a mass of dense cicatricial fibrous tissue with some bone and part of a synovial space showing chronic inflammatory changes. There was nothing suggestive of tumour. Five weeks later the patient died as a result of metastases in the chest. In the third case, in which amputation was performed early on radiographic evidence and without biopsy, the patient was progressing favourably a month or two later.

Bone development

Plasticity of bone

Discussion regarding causes.—In a Hunterian Lecture Brailsford¹ discusses the plasticity of bone. Young bones are able to withstand ordinary strains and stresses when ossification occurs in a normal regular and gradual manner, but if ossification is irregular, and multiple irregular ossific centres develop in the cartilaginous structure, it cannot withstand normal functions and becomes compressed and deformed, e.g. in hypothyroidism and in chondro-osteodystrophy. Plasticity may be due to generalized changes in the bones as in rickets and osteomalacia, and to those present in hyperparathyroidism with a parathyroid tumour in which profound decalcification of the skeleton ultimately occurs, or to changes commencing in one bone only as in Paget's disease. Fibrosis of bone or polyostotic fibrous dysplasia causes great deformity because of the plasticity developed by it. Localized plasticity of bone may be due to trauma when softening occurs and pressure causes deformity. Localized inflammatory lesions in or near bones lead to decalcification and plasticity, and immobilization is necessary in order to prevent deformity. In osteochondritis the plastic bone must be protected from pressure until reconstitution occurs in the affected part. Trauma can produce avascular necrosis of fragments of bone, and the most important feature is the accompanying osteochondritic reaction in the adjacent living bone. Failure to recognize such a reaction has caused many disasters subsequent to pinning of the fractured femoral neck. Any avascular fragment should be removed as soon as it is detected unless immobilization can be carried out until the fragment is reconstituted, that is, for 3-4 years. Radiography shows that sequestered bone retains hardness and sharpness of outline; tolerated fragments, however, undergo progressive decalcification and softening, and reactive changes in the adjacent bone lead to plasticity, a preliminary to reconstruction and consolidation. In contrast with septic sequestra, in aseptic necrosis the dead fragment is radiographically seen to collapse and break up within a few months.

Anderson, D. G., Howard, L. G., and Rammelkamp, C. H. (1944) *Arch. Surg.*, Chicago, 49, 245.

Behrend, A. (1945) *Ann. Surg.*, 121, 245.

Brailsford, J. F. (1945)¹ *Brit. J. Surg.*, 32, 345.

— (1945)² *Brit. J. Radiol.*, 18, 8.

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BRAIN: REGIONAL DIAGNOSIS

See also B.E.M.P., Vol. II, p. 609; and Cumulative Supplement, Key No. 188.

Disorders of function produced by disease or injury

Indirect symptoms

Anosognosia as a sign in two cases.—Roth describes 2 unusual cases of anosognosia, a

Adrian, E. D. (1944) *Brit. med. J.*, 2, 137.

Dawson, G. D., and Walter, W. G. (1944) *J. Neurol. Psychiat.*, 7, 119.

Roth, N. (1944) *J. nerv. ment. Dis.*, 100, 35.

BRAIN TUMOUR

See also B.E.M.P., Vol. II, p. 619; and Cumulative Supplement, Key No. 189.

Clinical picture

Bruns's syndrome

Alpers and Yaskin discuss the localizing and aetiological significance of Bruns's syndrome in neurological disorders. They describe in detail a group of 5 cases in which it was found —4 of neoplasm in the fourth ventricle or adjacent structures and one of disseminated sclerosis in which a plaque in the vermis might account for the syndrome—and they give a summary of 22 cases, in 19 of which a diagnosis of cystic tumour was confirmed. The symptoms comprising the Bruns's syndrome are periodic attacks of violent headache, vomiting and great vertigo, with in most cases a constant anterior flexion of the head, usually in the midline, but sometimes with lateral flexion and rotation. Any change in position of the head on the body, or even of the head and body in space, instantly evokes the subjective symptoms, to which tachycardia, "flashes of light", irregular respiration and true syncope with apnoea may be added. The severity of the symptoms varies: vertigo is a constant, headache and nausea are variables. Bruns considered the syndrome to be characteristic of a free or fixed cysticercus of the fourth ventricle, and for a time this was thought to be the case. Later observers, however, found additional causes, and it is now considered that the syndrome appears most commonly in intraventricular lesions such as ependymomata, medulloblastomata and astrocytomata of the vermis or, less commonly, of the cerebellar hemisphere with intraventricular projection, cysticercus cysts and papillomata of the choroid plexus of the fourth ventricle; occasionally it occurs with neoplasms of the third and lateral ventricles. The mechanism of the production of the syndrome is not clear. It has been supposed to be due to blockage of the ventricular system and obstruction of the cerebrospinal fluid. Alpers and Yaskin suggest that disturbance in the ventricular mechanism in the brain may be responsible for the symptoms.

Special methods of examination

X-ray examinations

Choroid plexus calcification and secondary pathological changes.—Wood reviews the established facts regarding pathological changes resulting from choroid plexus calcification and estimates their significance in relation to expanding intracranial lesions. The choroid plexus is a highly vascular fold of pia-arachnoid which produces the cerebrospinal fluid. Few pathological processes originate in the choroid plexus, tumours being uncommon. Cysts and psammoma bodies in the choroid plexus are considered to be of little significance and occur often after 40 years of age. These bodies vary in number and size; they are rounded and are made up of dense concentric fibrous layers. Possibly they arise from cysts in the plexus but authorities are not agreed on the mode of origin. It is important to recognize choroid plexus calcification and to differentiate it from a displaced calcified pineal body. It is now possible to localize calcium shadows in the choroid plexus with a great deal of certainty. Beals found that 28 per cent of a group of persons over 20 years of age show such calcification. It is usually symmetrical but it is important to recognize that an asymmetrical distribution of calcium is sometimes encountered. Calcification may occur in early life and in unusual places. Two such cases described are associated with mental deficiency. Physiologically, calcified intracranial structures, especially the calcified pineal body, act as landmarks in the diagnosis of brain tumours. Displacement of one calcified choroid plexus is occasionally the only evidence of an expanding intracranial lesion. Calcification may take the form of punctate shadows with the appearance of a cluster of tiny glass beads, or it may be linear or crescentic in outline.

Alpers, B. J., and Yaskin, H. E. (1944) *J. nerv. ment. Dis.*, 100, 115.

Wood, E. H., Jun. (1944) *Amer. J. Roentgenol.*, 52, 388.

BREAST DISEASES

See also B.E.M.P., Vol. II, p. 657; and Cumulative Supplement, Key Nos. 191–197.

Inflammations and their treatment

Acute mastitis and breast abscess

Incidence of mastitis in an industrial town.—Fulton emphasizes the difficulties involved in attempting to estimate the incidence of puerperal and lactational mastitis and reports on an investigation conducted in an industrial town in Scotland of 43,000 inhabitants and a municipal maternity hospital with 30 beds. An unofficial notification by health visitors of all cases of puerperal or lactational mastitis in their districts was introduced, so that any error resulting must have taken the form of an underestimation of incidence. Suppuration was the criterion of the presence of mastitis and the period covered was 2 years and 4 months. During the time mentioned 156 cases were notified, which amounted to almost 1 in every 10 recently parturient women in the town. Sixteen per cent of women delivered in hospital had mastitis in contrast to an incident of 3.05 per cent amongst women delivered at home. Only half the number of hospital patients were primiparae, so that factor alone could not be held to account for the high rate of hospital incidence. Most of the abscesses developed

after the patients' discharge from hospital, with a maximum incidence during the third puerperal week, 45 per cent of the cases occurred at the end of the fourth week. The author suggests that some of the following factors may explain the high rate of hospital incidence of the condition: (1) lack of immunity of the patient to organisms in the hospital or introduced into it by patients, staff and visitors, (2) acquisition by the infant in overcrowded hospital nurseries of micro organisms which are then transmitted to the mother, (3) general overcrowding in institutions, (4) milk stasis due to unduly long intervals (4 hours) between feeds and failure to feed from both breasts, (5) malnutrition of the hospital patient, who usually comes from a very poor home.

Tumours and their treatment

Malignant tumours

Folic acid (*Lactobacillus casei*)—Leuchtenberger, Leuchtenberger, Laszlo and Lewisohn have reported that 'folic acid concentrate' and a crystalline *Lactobacillus casei* factor are strong inhibitors of the growth of tumours. They now describe the effect of the *L. casei* factor (folic acid) on single spontaneous breast carcinomata in 120 mice living on a normal diet. The animals were divided into two equal and matching groups of 60, one group was given daily intravenous injections of 5 micrograms of *L. casei* factor for 4-6 weeks, the control group receiving no injections. No toxic effects were observed. A further 29 mice, which had no matched controls, also received injections. Results showed that in 38 out of 89 treated mice (43 per cent) the tumours completely disappeared, in only one animal did a fresh tumour develop. In the control group the tumours did not disappear and in 14 mice new growths developed. Observation of the animals was carried on for 2-10 months after treatment and during the period no recurrences were seen amongst the treated animals. It was also found that the treated mice lived longer than did the controls.

Aetiological influence of chronic cystic mastitis—In an attempt to evaluate the significance of chronic cystic mastitis in mammary carcinogenesis and to remove some of the confusion which arises from the inclusion in this diagnosis of multiple histological pictures, Foote and Stewart offer conclusions based on a study of 300 cancerous and 200 non-cancerous breasts. Macroscopic cysts are much commoner in non-cancerous breasts, and appear most often in the fifth decade a time of life when they are least common in cancer-containing breasts. There is no distinct difference in the commonness of duct papillomatosis but cystologically atypical papillomatosis is much more often found in cancerous breasts. Blunt duct adenosis is usually the precursor of cyst formation but is the starting-point of cancer in only very few cases. Apocrine epithelium is common in both cancerous and non-cancerous breasts and there are no outstanding differences in the two types of breast in relation to sclerosing adenosis, duct dilatation and periductal mastitis. The authors suggest that the true component parts of chronic cystic mastitis should include cysts, duct papillomatosis, of primary lobular alteration. Fibro adenoma is excluded. Statistical and morphological studies indicate that chronic cystic mastitis does play a part in the development of human breast cancer but the extent of its influence is unknown. In some people the papillary hyperplasias become uncontrollable and cystologically atypical. Foote and Stewart also comment on pathological findings in the breasts of 9 women treated with oestrogenic substances. It appears that the response to hormone therapy varies considerably with individual susceptibility. With one exception, oestrogens produced no noteworthy specific alteration in breast structure and no progressive series of changes beginning with a normal breast and ending with mammary cancer were encountered. In the one patient a lump which proved to be a cellular medullary infiltrating duct carcinoma was noticed in the left breast 6 months after the start of stilboestrol treatment. The composite structure of the breast proved to be unique in the authors' experience in that almost everywhere there were foci of sclerosing adenosis in florid phase. Merging with these lesions was much blunt duct adenosis in early proliferative phase. Duct papillomatosis was too, a prominent feature. Alteration in the mammary lobules was widespread and consisted in exact duplication of lactating breast tissue. Because of the exceptional nature of this case compared with others similarly treated, the authors hesitate to ascribe the development of the carcinoma to the effects of administration of stilboestrol.

Treatment by orchidectomy—The encouraging regression of the skeletal metastases from mammary carcinoma after castration in women who are still menstruating has suggested the possibility that orchidectomy might retard or even cause regression of mammary cancer in the male. Treves and his colleagues present the results of operation in 6 cases. They consider that bilateral orchidectomy may have been responsible for temporary regression of the primary lesion in 2 instances and possibly prevented local recurrence of mammary carcinoma in another case treated by local excision. The procedure clearly caused regression and repair in secondary deposits in bone and lung and there was dramatic cessation of pain caused by bone involvement, similar to that known to occur after orchidectomy in advanced cases of prostatic cancer. In the histological examination of the testes after orchidectomy, essentially normal gonads were found with no evidence of metastases. Changes which occur after administration of testosterone and α -oestradiol in the fluid and electrolyte balance, the nitrogen balance and serum protein fabrication, the urinary excretion of creatine and the utilization of carbohydrate, were not noted after operation. When cancer of soft tissues

metastasizes to bone, and attempts at repairs are made by the bone, the alkaline phosphatase of the serum rises and the metastases are osteoplastic. In cases in which no attempt at repair is made the alkaline phosphatase remains normal and the lesions are osteolytic. When bone destruction is very rapid, the calcium and phosphorus of the serum rise to high levels. The biochemical results in this series did not produce any evidence significantly demonstrating the effect of orchidectomy on bone lesions, such as usually occurs after the treatment of metastatic carcinoma of the prostate by the same operation. The authors admit the smallness of the number of cases under report and state that the value of the procedure can be determined only by observations on a larger group.

Other breast conditions

Abnormalities of structure

Essentials of success in mammaplastic surgery.—La Roe considers the factors that lead to failure in mammaplastic surgery. He deals with reconstruction of the pendulous, hypertrophic and atrophic breast. Mistakes of inexperience are not considered but rather those avoidable errors that do occur even with experienced surgeons. The blood supply and the histological structure of the breast require particular knowledge. It is axiomatic that success or failure depends upon the maintenance or not of an adequate blood supply. Failures are due to (1) haemorrhage, (2) liquefaction of fatty tissue, and (3) infection, sloughing and gangrene of skin, breast tissue or both areola and nipple. It is imperative to arrest completely the slightest bleeding or ooze of blood. Secondary haemorrhage often causes failure to obtain a good result. The commonest complication is the liquefaction of fatty tissue forming a sterile abscess accompanied by a rise of temperature. The abscess must be opened under the strictest aseptic precautions; the symptoms then usually will disappear. The sterile abscess formation must be distinguished from postsurgical infection, which should be treated like any other similar infection, supported by the use of sulphonamide drugs. Tissue necrosis results from interference with the blood supply leading to sloughing along suture lines usually in the upper lateral quadrant. In order to hasten demarcation of the necrosed area, infra-red radiation should be used. The most serious complication of all is the sloughing of areola and nipple. At the first sign of this, measures must be taken to increase the blood supply by removal of stitches, expulsion of blood clots, application of infra-red radiation, application of leeches and use of sterile compresses for the purpose of absorbing the blood.

General treatment

Prosthetic restoration

Artificial breast.—Brown describes in detail the technique of making prosthetic restorations of the breast in cases of amputation or of congenital absence or atrophy. The prostheses are of two types, (1) latex hollow pneumatic prostheses moulded in plaster of Paris, and (2) sponge rubber flexible elastic prostheses of commercial rubber, moulded under heat and pressure in aluminium moulds. For both types the breast or breasts are modelled in modelling clay, or in plasticine made with fine clay and olive oil, on a reproduction of the chest made of hydrocol, hard dental stone or similar suitable substance. In amputation cases the skin pores and details of the nipples are reproduced on the model by means of a plaster cast of the existing breast. In the case of latex prostheses the mould is filled with thick latex, mixed with suitable alkali-fast colour. After an interval the excess rubber is poured out, leaving a layer of rubber three-eighths of an inch thick. After hardening and trimming the finished article is elastic and resilient. In the case of elastic sponge prostheses the various ingredients are milled into sheets of rubber, these are cut into pieces to fit the bottom of each mould and are heated in aluminium moulds under pressure to 300° F., the rubber being thereby forced into every crevice of the mould and vulcanized at the same time. After removal from the moulds the rubber breasts are again milled, giving them the true sponge rubber consistency. They wear very well, and may be glued in place with a gum mastic mixture, or held in place by a brassiere, or both methods together may be used.

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La Roe, Elsie K. (1944) *Amer. J. Surg. N.S.*, 66, 339.

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BRONCHIECTASIS, BRONCHIOLECTASIS AND BRONCHIAL SPIROCHAETOSIS

See also B.E.M.P., Vol. II, p. 682; and Cumulative Supplement, Key Nos. 199–201.

Bronchiectasis

Aetiology

Bronchiectasis as a sequel to atypical pneumonia.—Kay describes 20 cases of bronchiectasis in the United States Army in patients who had had attacks of atypical pneumonia. Prior to the attack none of the patients complained of chest symptoms and x-ray pictures taken when they joined the Army were within normal limits. The author describes the aetiology and pathology of atypical pneumonia, emphasizing that the x-ray picture is usually at great variance with the mildness of the clinical signs and symptoms. He discusses the x-ray types

which have been described. It is commonly believed that bronchiectasis is an acquired and not a congenital disease, pathologically both bronchial and bronchiolar infection and occlusion, as well as interstitial pneumonitis, can occur, these being the factors which have been found experimentally to be necessary in order to produce bronchiectasis. Kay carried out repeated bronchography over a period of 6 months after the initial attack of atypical pneumonia and found that in all but 3 cases out of the series of 20 patients the bronchiectasis was permanent. In 10 cases lobectomies had to be performed in order to relieve the condition 6-13 months after the acute episode of atypical pneumonia. Reversible bronchiectasis occurs only if the bronchial walls are not damaged beyond repair by the initial disease and repeated bronchography is the only method of determining whether bronchiectasis is temporary or permanent. Kay describes the case histories of 7 of his series in detail and comments on the fact that the pathological examination of the affected lobes after lobectomy showed the permanence of the bronchiectatic process. In view of this complication he advises that patients with atypical pneumonia should be kept in bed until no abnormal clinical or radiological chest signs remain, and that prompt measures should be taken to relieve atelectasis if it appears.

Diagnosis and differential diagnosis

Value of x ray observation—Hinshaw, who considers that 'every patient who complains of cough should have roentgenographic studies of the chest', discusses the medical aspects of bronchiectasis which he emphasizes, can seriously involve the lung in the absence of recognizable shadows in ordinary skiagrams. The author advocates radiological investigation, repeatedly if necessary, after acute pulmonary disease in order to verify disappearance of all shadows. Bronchiectasis is a common sequela of recurrent bronchial obstruction. It is commonly associated with sinusitis, and before the fact was generally known sinus operations were often performed for relief of symptoms largely due to bronchiectasis to which the sinusitis was in fact, secondary. Differential diagnosis may be difficult. Hinshaw emphasizes obstructive lesions such as bronchogenic carcinoma, bronchial adenoma, foreign bodies, inflammatory bronchial stricture and lower lobe tuberculosis. For many years the sputum of every patient with productive cough has been examined at the Mayo Clinic. Owing largely to patients' failure to appreciate the significance of cough and expectoration of pus, most have had symptoms of bronchiectasis for many years before the diagnosis is made, the bronchiectasis is consequently too extensive for radical pulmonary operation. Medical treatment is satisfactory in less than 10 per cent of patients although encouragement and symptomatic relief can be given. The mechanism of drainage should be explained to the patient. It is not enough that he should lie flat across the bed with the head hanging over the edge, the hips must be high and the shoulders must be kept low with the thorax as nearly inverted as is possible. The use of chemotherapeutic agents administered by spray is undergoing clinical trial.

Treatment

Lobectomy—Alexander states that about 50 per cent of patients with bronchiectasis are suitable for lobectomy. Bronchiectasis occasionally disappears if the condition is due to stretching of the elastic bronchial walls without infection and in the presence of atelectasis. In general, however, since non surgical treatment is necessarily palliative, lobectomy is the only form of treatment that can produce a cure. Unqualified indications for the operation cannot be given but lobectomy is contra indicated if the lesions are extensive and bilateral. In certain clinics the mortality rate due to surgical intervention has been reduced to 5 per cent. The risk of lobectomy is least in children, and the removal of the lesions in childhood makes a normal life probable in place of a comparatively short life of varying degrees of illness. Efficient postural drainage is the most valuable of the palliative measures. Drainage should be carried out every 2 hours. Cycles of deep breathing and hard coughing should be repeated until the patient feels that no more secretion can be loosened by expectoration. Modified postures such as lying on the back, are suitable for patients who are too ill to adopt the inverted posture. The effectiveness of the drainage may be ascertained by a broncho-bronchoscopic examination, not only for diagnostic purposes, but also to aspirate secretions and to cause shrinkage of the bronchial mucosa by means of applications of Pantocaine (butethanol) and adrenaline. Aspiration aerates the peripheral portions of the affected lobes and this is accompanied by immediate changes in the physical findings. A bronchogram determines the presence of bronchiectasis but bronchoscopy reveals the nature of an obstruction. The instillation of iodized oil is of diagnostic rather than therapeutic value. The oil must not be instilled within 3 weeks after the disappearance of any febrile episode having its origin in the lungs. Removal of infection of the upper air passages may improve the symptoms but radical operations on the sinuses should be deferred until the late stages of treatment. Chemotherapy and allergic desensitization have proved to be useful only in exceptional cases.

One hundred cases of dissection lobectomy—Sellers, Thompson and Qvist summarize the results of 100 cases of dissection lobectomy for bronchiectasis. The dissection method of lobectomy differs from the hilum tourniquet method in that in the former all the hilar structures are ligatured separately. Permanent closure of the bronchus remains the chief problem and although various methods were attempted including pedicled intercostal muscle

graft, pleural or pulmonary flaps and sutures of silk and linen, bronchial fistula developed in 42 per cent of cases. As occlusion of the bronchus is so doubtful an issue it is not thought to be advisable to abandon primary drainage as a routine measure. In most of the authors' cases prior to operation, in order to bring about pleural adhesion to the upper lobe preliminary poudrage through the thoracoscope was undertaken with $\frac{1}{2}$ per cent iodized talc powder. The chief aim of any lobectomy must be to obtain rapid, complete and maintained re-expansion of the remaining lobe or lobes. This object is greatly assisted by the presence of adhesions. The more they obliterate the pleural sac the less likelihood is there of massive collapse. If secondary infection occurs with this latter condition the outlook is serious. In slow and incomplete expansion in the residual lobe empyema is inevitable and the prognosis is poor. Immediate and complete expansion took place in 56 of the 100 cases. Fifty of these gave good results, and in only 3 of the remainder could the unfavourable issue be ascribed to lobectomy. The commonest postoperative infection was tuberculosis, and secondary pyogenic infection was exceptional. Empyema was mostly secondary to bronchial fistula. Eighty-three per cent gave good results, and the operation mortality was 6 per cent. A hilar slough is inevitable in the tourniquet operation, and in the elimination of this lies the great advantage of the dissection method.

Surgical aspects.—Clagett considers that in the absence of serious contra-indications radical resection may be performed on patients aged from 4 to 40 years for reasonably well localized bronchiectasis. Although the best surgical risks are those in which only one lobe is involved, total pneumonectomy and bilateral lobectomy are possible. Surgical mortality of lobectomy for well localized bronchiectasis is about 4 per cent. Early diagnosis is imperative because the condition is more localized in young subjects; these tolerate operation better, and in a still growing patient true pulmonary tissue hyperplasia will restore the function of the removed lung segment. Operation should be delayed for 14 days after the use of radio-opaque oil, and the lung should be freed, as far as is possible, of secretions, by postural drainage. Pre-operative blood transfusion is indicated if anaemia is present. In the type of operation discussed by Clagett, nitrous oxide and ether are administered by intratracheal tube which permits of positive pressure anaesthesia and of aspiration of secretions from the trachea during operation. The sixth or seventh rib is resected through a posterolateral incision round the tip of the scapula and the pleural cavity is opened through the periosteal bed of the resected rib. The adhesions to the thoracic wall which are usually present are separated carefully in order to avoid tearing the lung and contaminating the pleural space. Hilar dissection and individual ligation of the pulmonary vessels are performed. After removal of the affected portion of lung the bronchus is closed with interrupted sutures and is covered with pleura. The remaining lobe is inflated with gentle positive pressure, a catheter is inserted for closed drainage and the thoracic wall is closed in layers. Bronchoscopy immediately after operation clears the bronchial tree. The patient, who remains in an oxygen tent for 24 hours, is encouraged to cough.

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BRONCHITIS AND BRONCHO-PNEUMONIA

See also B.E.M.P., Vol. II, p. 696; and Cumulative Supplement, Key Nos. 202-209.

Bronchopneumonia

Aetiology

Discussion of types and treatment.—On anatomical and pathological bases Adams questions the accepted classification of pneumonias in infants. A more accurate determination of the type of pneumonia is based on pathogenic causes of which more than one may be present. Fluid loaded with bacteria may be aspirated or may gravitate from the upper air passages into the lungs to play a part more important in the production of pulmonary disease than the inhalation of droplet infection. Virus infections such as the common cold, influenza and measles produce congestion, oedema and irritation in the lungs and so prepare the soil for the implantation of the pneumococcus previously present innocuously in the upper air passages of the infant. If the infant is laid prone in the cot, the end of which is raised by 12 degrees, such infection may be prevented and drainage of the tracheobronchial passages will be facilitated. Neonatal pneumonias may be caused by aspiration of amniotic fluid or vaginal secretion during birth. Treatment is by postural drainage and by use of the knee-chest position, with oxygen administration. Newly born babies should be placed in this posture so that tracheobronchial drainage may be promoted. It is possible too that such a position might tend to prevent the sudden death of babies in their cots (crib death), which hitherto has not been satisfactorily explained. It is important to protect from bacterial infection a young infant suffering from a virus disease. Chemotherapy, if used early, is of prophylactic value when smears show large numbers of bacteria. No striking results are observed from the use of chemotherapy in primary virus pneumonias. Damage to the structure of the lungs is caused by bacterial action preceded by a virus infection, a primary pneumococcal pneumonia affecting the structure very little. It is believed that the great variability of physical signs seen in pneumonia during the pandemic of influenza in 1918

was due to the various pathogenic organisms becoming involved with greater or less degree of virulence of the virus

Primary atypical pneumonia

General features of the disease—Karpel, Waggoner and McCown give a critical survey of 500 cases of primary atypical pneumonia. In the absence of x-ray facilities for chest examination this type of pneumonia may often go undiagnosed, some cases being very mild and asymptomatic. The cause of the disease is not exactly known, and little is known of its general incidence, but 500 cases were diagnosed out of 7,000 admissions to the New Orleans Medical Service Station Hospital. The onset is insidious and, in a moderately severe infection, may be malaise, chilliness, headache, rhinitis, sore throat and cough, with substernal pain or heaviness, or with unilateral pleuritic pain. Cough may be severe with tenacious mucoid sputum, sometimes blood stained. Fever, of septic type, may range from 102–104° F. In 4 per cent of cases abdominal pain was the chief symptom, some of these showed classical signs of appendicitis but there was a normal appendix on operation. The x-ray findings were diagnostic first, increased markings or increased peritroncal shadows compatible with a respiratory infection, secondly pneumonic infiltration. The characteristic finding is a soft shadow radiating from the bronchial trunk. An entire lobe may be involved, but usually only a portion of a lobe or lobes. In 52 per cent the right lower lobe was involved. Physical signs found were rales, harsh or suppressed breath sounds and impaired percussion note, absolute dullness being rare. Laboratory findings showed leucocytosis in about a quarter of the number of cases and leucopenia in 6 per cent. All blood cultures were negative and only a few pneumococci were occasionally found in the sputum. Complications were few, the most important being bronchiectasis, which seemed to develop with the infection. Prognosis was excellent. Sulphonamides were found to be completely ineffective and, there being no specific available, the general measures for combating systemic infections were employed.

General review—There appears to have been during the last few years an increased incidence of an unusual form of primary pneumonia which is refractory to methods of treatment specific for bacterial pneumonias and of which the aetiology is unknown. It is probably not a new disease and does not seem to be related to pneumonia of known virus causation such as ornithosis and influenza, nor is it apparently related to Q fever or to diseases of rickettsial origin. Gundersen discusses his experience of 122 cases, the majority of which occurred in the second or third decades of life. Cough, headache, malaise and sore throat were the symptoms most often encountered. The cough was characteristically explosive, hacking and distressing. "Prune juice" or rusty sputum was never noted and the typical pleuritic pain of pneumonia was absent. Night sweats occurred frequently and the fever, of irregular type, lasted on the average 9 days. Typical signs of consolidation were detected in less than one-tenth of the number of cases. Bacteriological examination of the sputa showed pneumococci in only 4 of 77 cases. Otherwise the findings were equivocal. Sulphonamides in adequate dosage produced no measurable effect. The diagnosis of pneumonia was confirmed by x-ray examination in all cases. The common site of involvement was the lower lung field and patchy areas of infiltration with indistinct borders were the most typical findings. There were, however, several cases of distinct lobar consolidation. A few of the films could easily have been interpreted as pulmonary tuberculosis. Treatment was symptomatic.

Pathological anatomy—Golden describes the pathological anatomy of acute interstitial pneumonitis, usually known clinically in the United States of America as "atypical pneumonia, aetiology undetermined". A large number of military and some civil cases were studied in the Institute of Pathology of the United States Army Medical Museum. The pathology was the same in all cases, whether of children, young adults or older persons. The pathological changes showed acute bronchiolitis, distributed focally, with desquamation of the mucosa occurring early. The bronchioles, which were often markedly dilated even in the early fatal cases, contained pus, mucoid fluid, and desquamated epithelial clusters or single cells, which were sometimes greatly disintegrated. In most cases no micro-organisms were found, although occasionally small numbers of bacteria were found in the bronchiolar pus. The walls of the bronchioles were infiltrated with mononuclear cells which extended radially into the peribronchiolar tissues, the alveolar walls and the pulmonary septa. The alveoli contained air or were collapsed, and unlike those in bronchopneumonia and lobar pneumonia, were relatively free of exudate. In some cases areas of coexisting bronchopneumonia, lobar pneumonia or pulmonary abscess were found. There is a strong presumption that interstitial pneumonitis is caused by a virus. Similar lesions are found in cases of acute influenzal pneumonia and also in measles, particularly in cases in which the patient dies within the first 5 days, presumably succumbing to the action of the virus before the onset of bacterial infection. In a few cases haemorrhagic brain lesions were found. There was no pathological difference between cases treated with sulphonamides and those not so treated.

In association with malaria—Fleming, Lindeck and Evans describe an epidemic involving 112 cases of primary atypical pneumonia, associated with malaria. The patients were admitted to a military hospital in Italy during the spring of 1944. The authors discuss the nature of atypical pneumonia and how often it passes unrecognized as bronchitis, bronchiolitis or pneumonitis. It is apparently a disease of temperate climates and of virus aetiology and is infective only during the incubation period which may be up to 12 days. Its association with malaria is probably fortuitous but several cases in the epidemic described showed an acute

onset resembling malaria and on the physical signs alone the patients might have been assumed to have malarial bronchitis. A high intermittent temperature for about 8 days was usual but the extremes were 1 and 24 days. The maximum incidence was in the younger age groups, a point also made in American reports. In the series reported by the authors cough was slight or absent in 61 per cent of cases. Twelve patients had no detectable physical signs throughout and showed minimal radiological signs. Each patient received an initial dose of 2 grammes of sulphapyridine or sulphathiazole, followed by 1 gramme 4-hourly for 3 or 4 days because, although these drugs do not affect the course of atypical pneumonia, the diagnosis is inevitably doubtful at first and their administration is in the nature of a therapeutic test and helps to prevent complications and secondary invasion. The authors urge that cases of malaria which appear to fail to respond to quinine should be most thoroughly examined both clinically and radiologically in order to exclude atypical pneumonia. They noted that simultaneous administration of a sulphonamide and of mepacrine hydrochloride may be ill tolerated but that no adverse effects were seen after the combination of sulphonamides with quinine, nor was there any toxic effect upon the polymorphonuclear leucocytes.

Summary of main features.—Wingsfield describes the diagnosis and treatment of primary atypical pneumonia. It is believed to result from a virus infection. The onset is insidious over a period of 2–4 days although in 25 per cent of cases it may be fulminant. There is a feeling of malaise with aching joints, unproductive cough and progressive rise of temperature. Pulse and respiration rates are not raised in proportion to the temperature and this comparatively slow pulse is an aid in diagnosis. Substernal pain is more common than is pleural pain. Rigors and dyspnoea are absent. Physical signs are few, indicating that the condition is not lobar pneumonia. Crepitations may be heard at the height of inspiration and indicate the site of involvement. Tubular breathing and aegophony are not heard. X-ray appearances are varied, usually showing a coarse and confluent mottling of the affected area. The illness may last 5–21 days and relapses are common. Treatment necessitates good nursing in a warm well ventilated room, and large amounts of fluid, preferably fruit juice with glucose, should be administered. The troublesome cough is relieved by the giving of codeine linctus or of diamorphine hypodermically. Sulphonamide drugs, which have no effect on the virus, are administered as a prophylactic against complications. Substernal or pleural pain is relieved by application of kaolin poultices or of an electric pad. Prolonged rest in bed may avoid relapse. Pleural effusion is the commonest complication. If the effusion is sterile or purulent from streptococcal infection at the first aspiration, the procedure should be repeated. If the fluid is pneumococcal in origin rib resection and drainage is required.

Review of current knowledge.—A paper on atypical pneumonia was contributed by the Commission on Acute Respiratory Diseases at a meeting of American bacteriologists in New York. The disease is an acute infection of the respiratory tract, presumably transmitted from person to person by contact, droplets or droplet nuclei. There is very little exact knowledge concerning it; it may be one disease or many diseases; it may have only one clinical form or many forms; it may vary from a mild infection of the upper respiratory tract to a severe and fatal pneumonia; it may be caused by one or many agents; it may be spread by direct contact or may be airborne in the truest sense. Clinically atypical pneumonia usually begins gradually with headache, malaise, fever and chilliness; there may be weeping eyes, running nose and sore throat, and later dry irritating cough. X-ray examination of the chest in most cases shows a pulmonary shadow indicating infiltration. Later there are physical signs of involvement of the smaller bronchioles and a productive cough. The illness may be short and mild, or prolonged and very severe. The aetiological factor is at present unknown, but voluntary human transmission experiments point to atypical pneumonia as being an airborne infection. Severe outbreaks have occurred in schools, colleges and military establishments; in the Army it appears to be endemic or sporadic. Atypical pneumonia has a relatively constant relationship to outbreaks of acute undifferentiated respiratory disease. No intermediary vectors, such as food or insects, have been found, and measures for the prevention of airborne infection give most promise of its control.

Chronic bronchitis

Aetiology

Climatic considerations.—Steel analyses the types of bronchitis, emphasizing the chronic form, the cause of so much absenteeism. He considers that a virus is the activating factor and that organisms in the sputum are probably secondary invaders. Cold and damp are important predisposing factors, largely through vasomotor effects, and the importance of adequate clothing for protection against sudden temperature changes is therefore stressed. Both hardening processes for children—especially bare heads, which cause great heat loss—and exposure of bronchitics to excess of fresh air, especially at night, are condemned; the author thinks that locality plays a big part in aetiology. Fifty-two per cent of 500 bronchitic patients inhabited coastal and low-lying areas. The congestive lung condition which is usually due to advancing myocardial damage predisposes the aged to bronchitis and its secondary infections. In discussing treatment Steel emphasizes the importance of dealing with upper respiratory tract infection and of removing adenoids and diseased tonsils from children, but advocates conservatism in other surgical procedures in the nose. Nasal sprays, for instance 2 per cent sulphathiazole and penicillin sprays, are of value for early morning sneezing, chronic sinusitis and multiple common colds. The author considers vaccines, in suitable small

Thirty-five patients with burns were examined and none had diabetes mellitus. Most of the patients were admitted to hospital within 2 hours of sustaining the injury. Any plasma or serum used in the treatment was glucose-free, and no proteins, fats, carbohydrates or vitamins were given during the period of study. Twenty-one patients were found to be in a hyperglycaemic state on admission to hospital. The level of the blood sugar, as determined by Folin's method, varied from 132 to 352 milligrams per 100 cubic centimetres. One patient, whose admission was delayed for 12 hours, had an initial level of 224 milligrams per 100 cubic centimetres. The incidence of hyperglycaemia was closely correlated with that of haemoglobin concentration and the extent of third degree burns. Glucose tolerance tests indicated that the added glucose could be utilized in spite of the presence of hyperglycaemia. Other blood tests showed an increase in the concentration of lactic acid and a moderate reduction in the carbon dioxide combining power of the plasma. A high degree of correlation was found between these abnormalities and the severity of the burn. There was no evidence that the burns were responsible for liver damage. In the presence of a normal liver any increase in the production of lactic acid may result in hyperglycaemia. It is suggested that the changes in carbohydrate metabolism may be associated with increased glycogenolysis and gluconeogenesis from protein but, in order to gain support for this view, it is necessary to estimate the glycogen reserves in the muscles and the liver. The blood sugar and plasma lactic acid are believed to be increased at the expense of the carbohydrate reserves of the body. This depletion should be remedied by the early administration of glucose.

Treatment

Tannic acid

Its effect on liver function.—Saltonstall, Walker, Rhoads and Lee discuss the effect of local methods of treatment, notably tanning agents, upon liver function and upon the mortality resulting from burns. Owing to the liver's large reserves and rapid powers of regeneration, function tests may not afford significant information until considerable liver damage has occurred. In their series of studies the authors utilized the van den Bergh reaction, the bromsulphthalein per cent retention at 30 minutes, the hippuric acid secretion test and the cephalin flocculation test, and a combination of these tests was found to provide an index that was fairly well correlated with the results of van den Bergh tests. Wells and his co-workers emphasized the hepatotoxic properties of tannic acid but since experimental animals, except fowls, do not blister, their burns and the effects of these are not comparable with human burns. Wells's results, however, considered in conjunction with the necropsy data cited by Erb, Farmer and Morgan, indicate that tannic acid used in burn therapy is sufficiently absorbed to increase hepatic damage. In the authors' series the average area of body surface burned was 33 per cent in the cases treated with tannic acid, 28 per cent in those treated by other tanning methods and 31 per cent in those treated by open methods. The clinical variations in burns make deduction difficult; the authors emphasize that in a severely burned patient there is such widespread injury that liver damage is probably rather a contributory than a determining cause of death; the general mortality amongst the untanned group in their series was 33·7 per cent and it was 20·7 amongst those treated with one or other tanning method. Tannic acid is the greatest hepatotoxic agent and other tanning methods have more hepatotoxic effects than have non-tanning treatments. Saltonstall, Walker, Rhoads and Lee believe that some degree of hepatic damage is always present as part of the toxæmia of burns but that it usually plays a minor part.

First, second, and third degree burns

Local treatment of second degree burns.—Dingwall and Andrus have studied local treatment in a controlled series of 82 second degree burns in human volunteers. The burns were bilateral and symmetrical and were produced by passing steam through a standard hollow metal plate for a constant time. In order to imitate the delay in treatment which usually occurs normally, no dressing other than sterile gauze was used for 24 hours. Thereafter the burn on one side of the body was dressed with a plastic film impregnated with a sulphonamide and the burn on the other side was treated with a different dressing, usually tannic acid or triple dye. In all, 12 substances were tested against the control treatment with Sulfafilm (3 milligrams of a sulphonamide impregnated into a methyl cellulose triethanolamine base). Results were assessed by rapidity of healing, absence of symptoms and freedom from all complications and were best in the burns treated with Sulfafilm. Escharotic agents, namely tannic acid and triple dye, required to produce healing a time usually twice or more as long as did Sulfafilm. Infection occurred most often with tannic acid and triple dye and the authors consider that their use should be abandoned. A series of cases which were treated with a bland ointment and with sulphonamides administered orally gave results nearly as good as did Sulfafilm. When Sulfafilm was used, those cases which were treated with a single dressing throughout healed in an average of just over 7 days. With 5 dressings nearly 14 days were needed—a significant argument against frequent dressings. Lesions in which all non-viable tissue was carefully removed healed no better than did those not so treated. Positive bacteriological cultures were often obtained but with Sulfafilm signs of inflammation were uniformly lacking. In the series in which boric ointment was used and sulphadiazine was given by the mouth, 4 out of 5 cultures were positive but no gross infection occurred. Complete elimination of infection as evidenced by persistently negative cultures does not therefore seem to be necessary for prompt epithelization of deep second degree burns.

Application of pressure

Experiments on goats—Cameron, Allen, Coles and Rutland describe the results of treating experimental thermal burns by the application of pressure. Twenty-eight goats were used for the experiments. 14 of which were treated with pressure, 14 were burned but were not treated. Nembutal (soluble pentobarbitone) was given intravenously for the purpose of eliminating pain and struggling and the burns, caused by water at 86° C were, in most cases, at once covered with quick-setting Cellon plaster bandages, applied fairly tightly. In a few cases the bandages were applied after 4-6 hours. In other experiments skin tight plaster was applied, exercising much less pressure. It was found that in extensive thermal burning, if this was untreated, blood plasma was rapidly lost into the burnt area, which was about 20 per cent of the total body surface. This was accompanied by haemoconcentration, slight transient haemolysis, slight increase in blood non protein nitrogen, decreased plasma and total blood volume and a steady decline in serum protein concentration. Pathological changes were found to be slight during the first 24 hours, haemolysed blood was excreted by the kidneys in small amounts and there was insignificant liver damage. When plaster pressure bandages were applied to extensive burns of the extremities haemoconcentration, loss of fluid and serum protein from the circulation and local oedema were reduced, and the clinical course was favourably affected. Delay in pressure bandaging caused inferior results, as did skin-tight bandaging although the latter was also useful. The observed facts can be explained most simply by assuming that pressure, through increasing the tissue pressure, combats the altered capillary permeability typical of a burn. Local plasma loss is reduced, plasma volume decrease is inhibited and the main danger of the first stages after burning is lessened.

The final stages

Preparation for skin grafting—Connor and Harvey discuss the problem of deep thermal burns in relation to the final stage of treatment, namely the grafting of skin at the earliest moment compatible with success and safety. The chief cause of delay is the continued presence of the slough and attempts to remove this by enzymatic digestion have recently been made. Local applications of acid, too, have greatly hastened separation by lowering the hydrogen ion concentration of the surface of the wound. Living tissue is not significantly damaged. In experiments on anaesthetized dogs, Connor and Harvey produced deep burns by gas flame. After burning, a dressing was applied of paste made of corn starch and pyruvic acid. Similar burns not so treated were used as controls and in these 10-12 days were required for separation of the slough. In the burns which were treated with acid, complete separation occurred in 72 hours. Separation began at the periphery and there then ensued a plane of cleavage beneath the slough which proceeded centrally. Dermal strands at the periphery were the last to separate, whereupon the whole slough was found to be separated in one piece. There was no digestion of the slough. The base consisted of pink living tissue with an excellent blood supply and took a split graft of skin immediately. Residual epidermal elements were not destroyed and adjacent epithelial cells little, if at all, damaged. The authors consider that infection and scar tissue formation with contraction can be obviated by this skin, its application to man is now being studied.

Skin grafting

Use of human plasma and thrombin—Clark, Milne and Todd successfully applied skin grafts in over 60 cases of burns, using for the purpose of fixation human plasma and thrombin, the preparation of which they describe. Plasma, separated from blood not later than 48 hours after its withdrawal from a group AB donor, is passed aseptically into sterile transfusion services should not be used. Thrombin is prepared by Herbert's method, namely by bubbling carbon dioxide through fresh plasma in order to reduce the pH to the isoelectric point at which prothrombin and fibrinogen are precipitated. After centrifuging, the addition of calcium chloride produces a fibrin clot and the thrombin can be decanted off in glass filter. Thrombin prepared in the manner described initiates the clotting reaction about 6 seconds after contact with fresh plasma. Dilution with sterile saline delays clotting. Donor and recipient areas are washed, successively, with 1 per cent Cetavlon solution, saline and ether. Lauberant granulations on the recipient area are trimmed with a sharp razor, plasma a dermatome, the drum of which is first coated thinly with pure Parafilm rubber, 5 per cent in carbon tetrachloride. The graft's raw surface is painted with thrombin solution and is applied to the recipient area, which has been previously painted with plasma. The authors claim that the technique ensures complete and continuous contact of the graft and the underlying tissues and controls the oozing of blood, and that the graft is fixed by means of a medium are not required to fix the graft in position. The advantage over Sano's method in which the patient's blood must be obtained prior to grafting, is that the materials are available from local transfusion services in a form ready for use.

General principles

Matthews discusses the treatment of serious burns and points out that no rigid rules can be laid down and that the selection of the method best suited to the individual case must be left to the man in charge. Certain principles, however, can be propounded. First aid

treatment consists in covering the burned area with sterile or at least domestically clean material and sending the patient to hospital. No form of local treatment should be instituted at the site of the accident. An exception should be made only in the case of minor, that is to say small superficial, burns, and even these should be classed as major in children and in old people. Hospital treatment includes general and local measures. The first essential is to save life. The danger is shock and this must be forestalled or treated. Local treatment is undertaken only if shock is absent; otherwise it is deferred until shock has been overcome. If the patient reaches hospital before shock has developed, local treatment is permissible after morphine has been given and a slow infusion of plasma has been started. The principles of local treatment are: (1) to prevent infection or to control it promptly if it is already present; (2) to preserve or restore the function of movable parts; (3) as quickly as possible to make the condition of the burned area suitable for skin grafting. Later treatment consists in promoting physical fitness and establishing a right mental attitude; both are of equal importance. The value of good nursing can hardly be overestimated. A high protein diet with a total calorie value of at least 2,500 is needed for cellular regeneration. Milk is a valuable source of proteins and can be taken through a tube when the mouth is burned. It also provides sufficient of the vitamins A and D. Vitamin B is best given in the form of Marmite and vitamin C in that of ascorbic acid tablets.

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CANCER

See also B.E.M.P., Vol. II, p. 737; and Cumulative Supplement, Key No 212.

Pathology and aetiology

Constitutional influences

Importance of hereditary influences.—Blank reports on constitution as related to cancer. From extensive survey of the biological background of malignant disease certain salient features emerge. Individuals of different constitutional types react differently to carcinogenic agents. Hormonal imbalance increases susceptibility to benign or to malignant tumours or to both. It is suggested that hereditary diseases are precursors of neoplasms and investigation along these lines is urged. Statistical evidence must be weighed with caution; owing to great incidence of malignancy in the general population deductions of inheritability should not be drawn from its occurrence in any given families. Weller, summarizing Waaler's statistically excellent work, says that "the incidence of cancer was significantly greater among the sisters of cancer patients than among the wives of the patients or in the general population. Among males the difference was considered inconclusive. . . . The proportional cancer mortality in the siblings varies with cancer incidence in the parental generation." Greenwood says that Waaler's findings are consistent with, although they do not prove, the truth of an hypothesis of the following type: (1) that some forms of cancer (for example lip cancer) are produced quite independently of any inheritable anlagen and that extrinsic factors have greater, perhaps exclusive, influence upon males; (2) that the heritable factors are two independent factors, both of which occur with a frequency of about 16 per cent. Various studies have led to the conclusion that cancer is not a unit disease because tumours of varying type and in different sites behave, genetically, in different ways. Tendency to a particular localization of malignant disease appears to be inherited. Amongst Wolff's 16 malignant cases 10 were instances of cancer of the breast; and mammary cancer can, by appropriate breeding methods, be developed in 90 per cent of mice of certain strong cancer strain in one of which, the R III, spontaneous mammary cancer has been shown to be associated with "brown degeneration" in the suprarenal glands—a process which Cramer and Horning attribute to breakdown of a mechanism which normally restrains the carcinogenic action of oestrogen on the mamma. Abnormalities of menstrual cycle may afford a clue to a high rate of cancer incidence in some families. There appears to exist a general inherited tendency to either susceptibility or resistance to tumour formation.

Experimentally produced cancer

Oestrogens and optimum age for administration.—Two experiments which were made in order to study the effect of the age at which the administrations of oestrogen was begun on the incidence of mammary carcinoma in mice, are described by Loeb, Suntzeff, Burns and Schenken. Oestradiol monobenzoate was administered to 77 male mice of the strains C₃H and D over a period of 5 months, treatment starting in groups of mice at the age of 2 weeks, 4–6 weeks, 1½–2½ months and 6–7 months. The authors found that mammary carcinoma developed only in the first two groups, the greatest incidence being in the second

group of the C₃H strain. In a second experiment oestrone was used, and the mice were male and female of the C₃H strain only, similar results were obtained in the male mice, but there was no significant difference in the incidence of mammary carcinoma in the different age groups. Loeb and his colleagues note that in the first experiment the period just prior and subsequent to sexual maturity was the effective period for the administration of oestrogen, if it were given later there was a sudden decline in effectiveness although the treatment extended over much the same period of life. The authors suggest that the possible explanation may be differences in growth, energy and readiness of sensitization between young and old tissues. Antagonism between male and female sex hormones may also be a factor.

Treatment

Review of modern methods

Souttar discusses team work in the treatment of cancer and points out that if the best results are to be obtained, coordination of effort between surgeons, radiotherapists, physicists and chemists is essential. With the surgeon should lie the establishment of diagnosis of the disease, estimation of its stage and probable progress and of dangers of surgical removal. A biopsy may be desirable but should not be regarded as a necessity. In certain types of case combined surgery and radiotherapy may be desirable, as in operable carcinoma of the tongue, the primary growth being surgically removed and the glands irradiated. By operations of access it may be possible in the future so to expose certain growths to radiation that there is not any risk to adjacent structures, as in disease of the lower end of the oesophagus or of the root of the lung or of the brain. When a cure has been almost achieved by irradiation the surgeon can often complete it by removal of the last remnant of the tumour. The radiotherapist should be a skilled diagnostician, but his chief contributions are an estimation of the therapeutic possibilities of a tumour, a full appreciation of the action of irradiation on normal tissues and a knowledge of remote consequences. It is to the physicist that the surgeon and the radiotherapist chiefly look for future developments in radiotherapy and to him is due the higher degree of accuracy now possible in all procedures. An increase in the voltage of x-ray apparatus would obtain higher energy and greater penetration, but the expense is great and too much space is required. The destructive effect of irradiation is limited to the individual cell. With the aid of the biochemist a substance may be discovered capable on absorption of destroying the cancer cell from outside. A team thus envisaged should draw up a schedule of cases and allot to each class clearly defined and appropriate methods of treatment. All methods worthy of investigation should be included. The team should decide the most appropriate method of treatment in each case. Every effort should be made to interest all doctors in the region. They can contribute largely to the work of the team and should realize the immense importance of early recognition of the disease.

Synthetic oestrogens in therapeutics

Haddow, Watkinson, Paterson and Koller report on investigations into the influence of synthetic oestrogens on advanced malignant disease. The production of tumours in animals by the use of oestrogens is readily brought about in those tissues which are very responsive to the physiological action of such compounds and which although possessing growth retarding properties may in certain circumstances induce physiological stimulation of growth or of carcinoma in other organs. The oestrogens triphenylchloroethylene, triphenylmethylene, ethylene and stilboestrol were used. Of 22 cases of mammary carcinoma which were treated with daily doses of 3-6 grammes of triphenylchloroethylene, 10 showed a temporary retardation of growth, but this was less than could be expected from local palliative irradiation with x rays. The initial effect passed off comparatively rapidly. One case only showed prolonged arrest, the other cases did not show any alteration. The development of metastases was not affected. Of 30 cases similarly treated, of carcinoma of the skin, maxillary antrum, urinary bladder, ovary, rectum and testis, with reticulo-endothelial growths and leukaemia, 2 cases only showed partial regression. These were a carcinoma of the bladder and a carcinoma of the prostate. Triphenylchloroethylene was given intramuscularly in 4 cases of response. Stilboestrol, given orally or intramuscularly in 14 cases of mammary carcinoma, produced similar effects to those of triphenylchloroethylene. Secondary signs of drug action were nausea, pigmentation of the mammary areola, mastitis in the male, uterine bleeding and oedema of the legs. Some of such changes tended to occur more often in cases showing any regression and in these patients there was sometimes improved appetite and weight and carcinoma which were made during a period of tumour regression after administration of stilboestrol. There was diminished mitotic rate and an increased number of degenerating cells the morphology of which differed from that of cells degenerating as a result of x-ray or γ -ray irradiation. Nuclear vacuolization and breakdown in mitotic mechanism were seen, with variations in staining. In this particular instance the cytological evidence suggests that the primary effect of the stilboestrol may be localized to the nucleus of the tumour cell.

Prophylaxis

Need for controlled nutrition and exercise—Potter stresses the importance of controlled nutrition with exercise in cancer prevention. The incidence of cancer is increasing and it is suggested that overfeeding and underexercise are together a real cause of cancer. The rate

of incidence of cancer is much higher among diabetics than among the general population. Cancer is part of the price paid for modern civilization. When laboratory animals are placed under analogous conditions, the incidence of cancer among them increases. The public expect and await a cure for cancer by the dramatic discovery of a chemotherapeutic substance or some agent such as penicillin, with selective action against cancer growth. It is unlikely that such a discovery will happen by chance; it will be made as the result of sustained effort over many years. Much knowledge has accumulated since cancer was successfully transmitted from one animal to another. Carcinogenic agents have been detected in coal-tar and in ultra-violet light and by means of the ingestion of certain compound bodies in the diet. The development of cancer can be marked by three stages: (1) an induction period, the result of the presence of cafcinogens; (2) a critical period, affected by irritation, injury, calorie intake, exercise; (3) a progressive period, the result of release from restraint of normal cells. Feeding experiments on groups of mice show that animals on a low calorie diet when subjected to carcinogenic stimuli are very resistant to the development of cancer; the calorie effect operates during the second phase of development. Normal cells possess a self-regulating mechanism in the process of tissue repair, and the cancer cells are susceptible to restraint by normal cells. If restraint is maintained the cancer cells regress; if it is not, the cells develop into cancer tumours. With a low calorie diet the energy of trained cells can compete with cancer cells during the critical period. Only food required for physical fitness should be eaten.

Discussion on post-war treatment

In opening a Discussion in the Section of Radiology of the Royal Society of Medicine, on post-war organization for treatment of cancer, Carling stressed that any cancer scheme must provide for diagnosis, surgical treatment and radiotherapy. A single radiotherapeutic organization was known to require a population of about 2,000,000 for its best development; there had been recent experience of expert services such as those of orthopaedics and neurosurgery operating successfully over similar large areas, into about 12 of which regions the country, excluding the London area, could be divided. Such areas, each containing a university city as natural headquarters and a number of smaller districts should, the speaker suggested, be utilized for the development of special cancer surgical services. At the periphery of each region every suspected case should be registered—the equivalent of notification—at preliminary investigation centres. Notifications should reach a central bureau, the director of which would correlate all records and ensure that all patients were treated by the appropriate person. Diagnosis was the function of the consultative out-patient department of the large general hospital. Once diagnosed, the cancer case would normally be treated in the principal "district" hospital. Surgical specialists would be the most successful operators for cancer situated in their particular anatomical region. The help of the headquarters team, selected from the most experienced surgeons, specialists, radiotherapists, pathologists and physicists of the area or region, should be at the service of the district associates who should, in turn, serve the general practitioners. In clinical and research matters, cooperation among the whole staff of the area organization was important. The public must be told that small administrative authorities would not supply the best services possible, and that these could be given only by a large regional organization. Other speakers agreed that the teamwork and cooperation necessary throughout could be obtained only by concentrating cancer treatment in large centres based on the universities, with affiliated centres in smaller towns. Stebbing advocated a regional organization having a whole-time director—possibly a pathologist—and headquarters in a general hospital in which there was a highly organized radiotherapy department. Voluntary and local authority hospitals should cooperate in each regional organization. Nuttall favoured a complete cancer service with its own distinct organization within the framework of a teaching hospital. A comprehensive cancer service, it was further suggested, would require well-trained medical, technical, statistical and administrative workers, nursing facilities for incurable cases—whose numbers "cancer propaganda" might decrease—and hostels in association with diagnostic and treatment centres to care for ambulant patients.

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CARRIERS IN INFECTIVE DISEASE

See also B.E.M.P., Vol. II, p. 755; and Cumulative Supplement, Key No. 215.

Detection, cure and care of carriers

Prevention of cross infection

Nursing of infants undergoing plastic surgical treatment.—Pickerill and Pickerill consider that the treatment of illness in hospital is fraught with the risk of the patient acquiring a fresh infection. The danger is greatest among children. In infants requiring plastic operations the raw surfaces are traps for all types of infective organisms floating about a hospital ward. For this reason the authors decided to have the infants nursed by their mothers either in

their own homes or elsewhere. The rationale was based on the fact that a baby has a certain degree of immunity to its mother's organisms. The procedure resulted in a reduction of cross infection by about 75 per cent. Greater success was achieved after a house had been acquired to accommodate 12 mothers and babies. A small theatre block was built in the garden and a large workshop was converted into an isolation ward. The mothers were invited to come to the house and to nurse their babies just as if they were at home. Between operations the infants were nursed out of doors as much as possible. Every endeavour was made to ensure that the mothers were happy, for a disgruntled mother causes discontentment in the baby and thereby jeopardizes the outcome of the operation. Postoperative antiseptics were not used, so that absence of infection could not be attributed to their use. During the course of 3 years there was not a single case of cross infection and no failure occurred with any case of cleft palate, hypospadias, angioma or syndactyly.

Prevention of droplet infection

Mitman states that the horizontal distance over which micro-organisms can be transported is almost limitless. The effective range, however, is determined by the ability of the organisms to survive, since pathogenic bacteria have never been recovered from the upper air or from marine air. Most human respiratory infections take place indoors as a result of pollution of the air by droplets, dust and discharges. The number of dust particles greatly exceeds the number of organisms. Sneezing adds a very much greater bacterial load to the air than does coughing or talking, but most of the droplets are expelled from the mouth. The droplets rapidly evaporate into nuclei consisting of individual bacteria, small masses of organisms or viruses on a minute film of water. Droplets can infect the upper respiratory tract, but only the nuclei and a few dust particles can reach the alveoli of the lungs. There is an extensive interchange of respiratory flora in overcrowded public transport vehicles. Many journeys could be avoided if houses were built closer to the centres of employment. The recent increase in the use of the pocket-handkerchief has reduced the incidence of respiratory infection. The use of blankets is undesirable in hospital because they spread infection. The results of oiling the bedclothes and floors are not impressive, but efficient and comfortable masks would prove to be of value. Air-conditioning does not produce complete disinfection of the atmosphere, and there are limitations in the use of ultra-violet irradiation of the air because the radiations are of poor penetrating power, especially in the presence of dust.

Carners in special diseases

Streptococcal infection

Cross infection and its control—Wright reports an investigation in which the risks of cross infection were assessed among patients with measles who were treated in hospital. Cross infection was judged to have occurred if a patient acquired haemolytic streptococci in the nose and throat. More than 90 per cent of the infections were due to the type VI haemolytic streptococcus. During the course of 12 weeks 47 of 65 patients acquired this organism in the upper respiratory tract. In spite of chemoprophylaxis middle ear suppuration ensued in 18.5 per cent of cases. Operations for mastoiditis were required in 4 patients and, in each instance, the type VI streptococcus was recovered from the mastoid process. Infections of the skin, especially impetigo, developed in 26 per cent of cases. Allowing 14 days as the normal stay for the patient in an uncomplicated case of measles, the total excess stay in hospital amounted to 2½ years. Among 496 patients, in 3.6 per cent middle-ear suppuration developed during the first 5 days of treatment, whereas 13.3 per cent of cases showed signs of the complication during the later stages of the illness. It is assumed that most of the late middle-ear complications were due to cross infection. In view of the findings treatment at home rather than in hospital is advocated for patients with uncomplicated measles. If these patients are admitted to hospital, it is essential to prevent streptococcal infection spread by contact, droplets and dust. Overcrowding must be avoided, especially in the case of infants.

For the purpose of elucidating the problem of cross infection in hospital wards, Hamburger made a study of the dispersal into the surrounding atmosphere, by means of saliva droplets, of haemolytic streptococci by infected persons. Cultures were made from the manifestly inflamed throats of 76 patients and from those of 80 scarlet fever patients, cultures at the same time being obtained from the saliva after considerable dilution. The terms, positive and negative, are used not in an absolute but in a comparative sense only. In talking and laughing, as well as by sneezing and coughing, patients expel droplets of saliva. Generally the more positive the throat infection, the more likely will haemolytic streptococci be found in the saliva. The number of haemolytic streptococci in the saliva falls gradually as convalescence proceeds and more rapidly after the fifth day in hospital. Saliva of patients who have had their tonsils removed generally contains fewer haemolytic streptococci than does that of those with tonsils. The same serological type of streptococci are found to be present in the throat and in the saliva. The oral administration of the sulphonamides has no permanent effect on the number of streptococci in the throat or in the saliva. Haemolytic streptococci carried in the nose are potentially more dangerous than are those which are present in the saliva. It is a matter of interest that the haemolytic streptococcal content of the saliva is much the same in cases of tonsillitis or pharyngitis with a scarlet rash as it is without it. This observation supports the view that these conditions are identical.

Hamburger, M., Jun (1944) *J. infect. Dis.* 75, 71.
Mitman, M. (1945) *Brit. med. J.* 1, 71.

Pickerill, H. P., and Pickerill, Cecily M. (1945) *Brit. med. J.*, 1, 159.
Wright, Joyce (1945) *Brit. med. J.*, 1, 285.

CATARACT

See also B.E.M.P., Vol. III, p. 1; and Cumulative Supplement, Key No. 216.

Acquired cataract

Senile cataract

The somersault operation.—Pahwa, who has performed 170,000 operations for cataract, describes his method of intracapsular extraction. The advantages claimed are simplicity, freedom from complications and small amount of instrumentation; the method is suitable for all types of senile cataract. The steps are as follows. Under local anaesthesia a speculum is inserted and the eyeball is fixed with fixation forceps. For the right eye the knife is inserted at 9 o'clock in the cornea at the side of the limbus conjunctivae, carried straight across the anterior chamber and brought out at 3 o'clock. For the left eye the places of entry and exit are 3 and 9 o'clock respectively. The knife is carried straight upwards and the section is finished about 1 millimetre below the upper border of the cornea, i.e. the section is made rather low. The iris is pulled out through the wound and is cut with scissors. The speculum is now removed. The assistant pulls the upper lid upwards with a strabismus hook and the lower lid downwards with his fingers. A strabismus hook is applied to the sclera 2 millimetres below the junction at 6 o'clock. It is slowly drawn up towards the limbus with very slight backward pressure, thus dislocating the lens, which turns a complete somersault and is delivered lower pole first through the corneal section. The iris is replaced. The upper lid is lowered gently, the eye is covered with cotton wool and both eyes are bandaged. The patient is warned in advance against closing the eyes tightly or squeezing the eye.

Pahwa, M. D. (1944) *Arch. Ophthalm.*, N.Y., 32, 48.

CELLULITIS

See also B.E.M.P., Vol. III, p. 11; and Cumulative Supplement, Key No. 217.

Clinical picture

Constitutional symptoms

Pyrexin, a pyrogenic factor.—Menkin reports observations on the chemical basis of the pyrexia which accompanies inflammation. The author has, in previous investigations, demonstrated the pressure in inflammatory exudates of necrosin, a substance which either is the euglobulin fraction of the exudate or is associated with it; when introduced into the blood stream necrosin causes a prompt leucopenia followed, several hours later, by a leucocytosis. The process injures internal organs, notably the liver and kidneys, in which there occur fatty deposits in the parenchyma and scattered small foci of leucocytic infiltration. Intravascular injection of necrosin leads also to rapid rise of temperature which is not induced by other protein fractions from exudate or by ascitic fluid or normal blood serum. Purified necrosin is, however, non-pyrogenic. The author's recent investigations suggest the presence in inflammatory exudate of a pyrogenic factor which is associated with the euglobulin but is apparently a proteolytic split product formed by the action of necrosin; necrosin seems to be either a proteolytic enzyme or displays—in its present state of purification—proteolytic activity. The pyrogenic factor, termed pyrexin, appears to be an end product of enzymatic activity associated with necrosin, and has a nitrogen concentration of about 11 per cent and a total phosphorus concentration of about 11 per cent. It is insoluble in distilled water, in isotonic sodium chloride solution or in presence of ammonium sulphate or in strong acid. It is soluble in relatively weak alkali. It is indiffusible and heat stable. Necrosin is soluble in the presence of sulphate ions. Pyrexin is absent from normal non-haemolysed blood serum but is present in haemolysed serum and in the serum of an animal in which an inflammatory process is active. In investigations on dogs a pyrogenic factor, probably pyrexin, was recovered from their urine in amounts which increased with the progress of an inflammatory reaction in the pleural cavity. Pyrexin probably acts upon the hypothalamic heat-regulating centre.

Menkin, V. (1945) *Arch. Path.*, 39, 28.

CEREBELLAR DISEASES

See also B.E.M.P., Vol. III, p. 21; and Cumulative Supplement, Key No. 220.

Cerebellar atrophies

Atrophy of cerebellar cortex

Familial cortical atrophy in three generations.—Hall, Noad and Latham describe a type of familial cortical cerebellar atrophy as seen in a family in Australia. The original pair came from Germany about 75 years ago, and of their 5 children 4 were affected by the disease. In the third generation 5 members are affected, 1 is "suspect" and 2, who were unaffected, died early. Most of the 17 members of the fourth generation have been examined and one has been found in whom the disease is likely to develop. Some members of a branch descended from a member of the second generation are also known to be affected. The age of onset is indefinite; the middle fifties was the prevalent age in the second generation and approximately 40 in the third. Longevity is not appreciably affected; the onset is insidious and the progress very slow. The initial symptoms are always disturbances of gait or of speech, the ataxia being typically cerebellar and the dysarthria varying between a slight slurring of words and complete unintelligibility in the later stages. The voice is high pitched and monotonous. Muscle tonus remains normal and tendon reflexes are unaffected; nystagmus usually makes

its appearance later. Difficulty in swallowing was found in 3 cases. In the early stages, in the majority of cases, a diagnosis of "joint disease" had been made, but no evidence of such was found. The chief pathological findings were those common in hereditary states, namely a wholesale generalized degeneration of all the Purkinje cells of a centrifugal type, with greater prominence of the basket system and certain glia, as well as grave destruction of the olive neurones with severe compensating gliosis therein. Otherwise apart from some presumably arteriosclerotic changes, all other parts of the brain showed nothing pathological. The primary familial group into which these cases and others described in the literature fall, differs entirely from examples of cerebellar disease described as olivo-ponto-cerebellar atrophy.

Hall, B., Noad, K. B., and Latham, O. (1945) *Med J Aust*, 1, 101

CEREBRO-RETINAL SYNDROMES OF THE HEREDO-DEGENERATIVE TYPE

See also B E M P, Vol III, p 30, and Cumulative Supplement, Key No 222

Clinical types

Tay-Sachs's disease (infantile amaurotic idiocy)

Endocrine gland changes—Marburg describes the changes found in the suprarenal and thymus glands in 3 cases of amaurotic family idiocy. He considers that the so-called pareses of this disease are in reality asthenias, the affected muscles having normal electric reaction and normal tendon reflexes. The 3 patients examined were aged 1½ years, 3 years and 1½ years, two boys and a girl. All 3 showed identical signs and symptoms of asthenia and idiocy, with optic atrophy and cherry red spot, in all the illness had lasted for under 2 years and all 3 children died of pneumonia without becoming cachectic. The suprarenal glands showed marked lack of medulla in all cases. A relative hyperplasia of the thymus gland was found, and increase of colloid in the thyroid gland, there was a prematurity of the gonads with degeneration of the interstitial cells. Other glands were found to be normal, the pancreas being well developed, with numerous islands of Langerhans. This may account for the adiposity found in most children at the beginning of amaurotic family idiocy. Discussing the findings of other observers recorded in the literature with those of his own 3 cases, Marburg considers that the asthenia in amaurotic family idiocy may be regarded as of the same type as that in myasthenia, Addison's disease and toxic goitre, myatonia congenita and familial periodic paralysis. Myatonia may perhaps belong to this group also. These asthenias may be called endocrine dysergias and anergias, caused probably by disturbances in the acetylcholine mechanism, as proved by the effect of Prostigmin in myasthenia. These disturbances in turn may be due to lack of suprarenal medulla in Addison's disease, amaurotic family idiocy and perhaps toxic goitre, the hyperplasia of the thymus gland being perhaps compensatory for the lack of suprarenal medulla.

Marburg, O. (1944) *J nerv ment Dis*, 100, 450

CEREBROSPINAL FEVER

See also B E M P, Vol III, p 39, and Cumulative Supplement, Key No 223

Clinical picture

The fulminating form

Waterhouse-Friderichsen syndrome in adults—The Waterhouse-Friderichsen syndrome is more common in children than in adults, but Cosgriff describes 4 adults whose illnesses coincided with an epidemic of meningococcal meningitis. The condition arises from various forms of severe sepsis but especially from meningococcal infection. The illness was fulminating in all 4 cases and was characterized by pyrexia, shock, hypotension and purpura. Conjunctival bleeding caused the unusual manifestation of haemorrhagic tears. Signs of meningeal involvement were noted in one case, cyanosis and coma preceded death, and necropsy showed generalized purpura with haemorrhages into the suprarenal glands. In 3 patients blood culture was positive for *Neisseria meningitidis*. Analyses of the blood in 2 cases showed a decrease in the serum sodium and an increase in non-protein nitrogen. The findings were compatible with adrenocortical insufficiency but necropsy in one of these cases showed only a small number of haemorrhagic extravasations into the cortex. Moreover, the patients did not respond to the administration of adrenocortical extract, fluids and electrolytes. The failure of specific treatment may indicate that hypo-adrenalism was a secondary rather than a primary cause of death. Hypotension, dehydration and vomiting are manifestations not only of hypo-adrenalism but also of an acute overwhelming infection with widespread tissue damage. It is recommended that treatment should be directed towards overcoming infection by administering sulphadiazine, or penicillin or its related substances. Additional therapy with adrenocortical extract is advisable, however, because it has been demonstrated that infections cause an increase in the urinary excretion of hormonal substances, presumably of suprarenal origin.

Treatment

Penicillin

Comparison with sulphonamide therapy—Meads, Harris, Samper and Finland discuss the treatment of 9 cases of meningococcal meningitis with calcium penicillin, given both intrathecally and intramuscularly. The patients' ages ranged between 14 and 58 years, the average duration of the illness before admission to the Boston City Hospital being 3 days. One patient

only had had an oral dose of sulphadiazine before admission. Lumbar puncture with full examination of the cerebrospinal fluid was performed and blood and throat cultures were made on admission, in all cases. Penicillin therapy was started immediately, the initial intrathecal dose being 10,000–20,000 units in 10 cubic centimetres of physiological saline; then 5,000–15,000 units were administered at 12-hour intervals until improvement took place; the dosage was continued at 24-hour intervals until recovery, the total amount given being between 30,000 and 150,000 units. Simultaneously, intramuscular penicillin was given in 10,000–15,000 unit doses at three-hour intervals for 2½–6½ days depending upon the rate of recovery; the total dose was 190,000–1,155,000 units. Group I meningococcus had been identified in 8 cases in the cerebrospinal fluid and in 4 cases in the nasopharynx. Six patients improved after 1–5 days' treatment and became afebrile in 5–15 days. The patient who had received sulphadiazine before admission recovered after 3½ days' treatment and 2 cases showed clinical recurrence after treatment but responded rapidly to standard doses of sulphapyrazine. The strains of meningococcus isolated varied in sensitivity to penicillin, but all were sensitive to sulphadiazine. Tests showed that the levels of penicillin in the spinal fluid after 10–12 hours were quite sufficient for bacteriostasis. The authors conclude that comparison with the results given by treatment with sulphonamides suggests that they are the compounds of choice in the treatment of group I meningococcal meningitis, and that penicillin in the doses mentioned may be effective in the treatment of this type of meningitis although the response is not as good as is that when sulphonamides are used.

Cosgriff, S. W. (1944) *Ann. intern. Med.*, 21, 187.

Meads, M., Harris, H. W., Samper, B. A., and Finland, M. (1944) *New Engl. J. Med.*, 231, 509.

CERVICAL RIB

See also B.E.M.P., Vol. III, p. 75.

Evidences of nerve compression

Vascular effects

The scalenus syndrome.—Love reviews the scalenus anticus syndrome with or without cervical rib. Prior to 1927 the cervical rib itself was believed to be the cause of the syndrome. In many cases, however, the anomaly was accidentally discovered to be present without producing symptoms. Adson called attention to the part played by the scalenus anterior muscle in the production of the syndrome and to its relief by section of the muscle. He recommended an anterior approach in the surgical treatment even if a cervical rib was to be removed. The syndrome rarely occurs before adult life. Adson is of opinion that the muscle produces compression of the subclavian artery and brachial plexus during the height of its activity in adult life, which, since most people are right-handed, explains the greater frequency of right-handed symptoms. The insertion of the scalenus anterior muscle is invariably wide in cases in which the syndrome appears. The pain is sharp and shooting and is aggravated by sudden rotation of the head or forceful depression of the shoulder or it may be a dull aching pain distributed over the ulnar and median nerves. Circulatory involvement is indicated by the diminished volume of the radial pulse which can be obliterated by elevation of the chin and rotation of the head to the affected side while taking a deep inspiration. Circulatory signs may simulate Raynaud's disease. There is marked supraclavicular tenderness on pressure. If palliative treatment fails, surgical section of the scalenus anterior muscle should be carried out, with or without the removal of any existing cervical rib.

A new neurovascular syndrome.—Pressure on the subclavian artery and brachial plexus causing paraesthesias and impaired circulation may be produced by obvious bony abnormalities such as cervical ribs and extended transverse processes, by their cartilaginous or tendinous counterparts, and by the so-called scalenus anterior syndrome. Wright now discusses a neurovascular syndrome produced by hyperabduction of the arms, which is capable of causing gangrene by occlusion of the subclavian artery, and sensory disturbances probably due to stretching, torsion and ischaemia of the brachial plexus trunks. These stresses appear to occur predominantly (1) at the point at which the axillary subclavian vessels and plexus trunks pass behind the pectoralis minor and beneath the coracoid process and (2) at the point at which the subclavian vessels and plexus trunks pass between the clavicle and first rib. Wright mentions a number of patients in whom the syndrome developed after they had, over periods of months or years, assumed in sleep the supine position with arms hyperabducted; in others it followed occupational hyperabduction. In more than 80 per cent of normal people it was possible to find, by experimental hyperabduction of the arms above the head, a point at which obliteration of the pulse occurred; in certain instances the pulse was present intermittently. The position of the head also affected the obliteration of the pulse in some people, suggesting involvement in the same group of the scalenus muscles. In Wright's opinion, however, it is erroneous to use hyperabduction of the arm as a test for the scalenus anterior syndrome for in such a position the scalenus muscles are relaxed rather than tensed. It is concluded that occlusion of the subclavian artery by hyperabduction of the arms is a natural phenomenon and that those people in whom it occurs should refrain from maintaining the position either in work or in sleep. There are obvious risks for such people whose arms are in hyperabduction on operating tables or are held in the position by splints or casts.

Love, J. G. (1945) *Proc. Mayo Clin.*, 20, 65.

Wright, I. S. (1945) *Amer. Heart J.*, 29, 1.

CHANCROID

See also B E M P, Vol III, p 97, and Cumulative Supplement, Key No 227.

Treatment*In the Tropics*

General management—Satulsky discusses the management of chancroid in the Tropics and reports on a series of 1,555 cases, in which the average incubation period was 3-10 days. Multiple lesions were present in 1,160 patients and single lesions in 390. Diagnosis was made on clinical grounds after elimination of complicating diseases, principally syphilis. On admission to hospital the patient was treated by saline compresses applied locally and rest in bed. At least 3 daily dark-ground studies for syphilis were made. The diagnosis is difficult when the two diseases coexist. Serological studies were made and all soldiers had 3 further monthly tests for syphilis. When enlargement of the lymph glands was present a Frei test was done. Sulphonamide therapy was the treatment of choice and greatly reduced the duration of the disease and the complications. Circumcisions and other operative procedures were avoided during the active phase and circumcisions after a cure were delayed for at least 3 months. Soft fluctuating inguinal glands were aspirated through a cannula and 1-1.5 cubic centimetres of 7 per cent tincture of iodine were instilled through the cannula, which was left *in situ*, for 3-4 days a pressure bandage was applied and the patient was kept in bed. After having been thoroughly washed and dried the ulcer was dusted twice daily with sulphanilamide powder until it had healed. For oral administration when indicated sulphathiazole was found to be the most efficacious drug, 1 gramme 4 times daily for 5 days and then 0.5 gramme 4 times daily for 10 days being the dosage used. All lesions healed under the therapy with an average stay in hospital of 11.2 days.

Satulsky, E. M. (1945) *J. Amer. med. Ass.*, 127, 259.

CHILD GUIDANCE

See also B E M P, Vol III, p 125.

Aetiology of behaviour disorders*Grouping of aetiological factors*

Value of electroencephalographic investigation—Gottlieb, Knott and Ashby describe the results of a study of the electroencephalograms of 67 children with primary behaviour disorders. It has been often shown that there is a high incidence of abnormality in the electroencephalograms of such children, and in this series of children, none of whom showed signs of organic disease and in none of whose conditions an organic factor was suspected, 49 per cent had electrical brain potentials which were clearly abnormal. This abnormal type may be subdivided into 3 groups: (1) in which the abnormal electroencephalogram may be related to a family history of psychosis, maladjusted personality, chronic alcoholism or epilepsy, illness or convulsions, (2) which is related to a personal history of prematurity, birth injury, head injury, severe operate. The abnormal electroencephalographic record implies the presence of some pathological physiological process, but a normal record does not necessarily mean that such a process is absent for it may be dormant at the time of recording. The statement, furthermore, applies only to the cortex since deep lesions may be proved to be present with normal electroencephalograms. It is therefore probable that an unknown number of patients show primary behaviour disorders with normal electroencephalograms and yet have pathological neural function. The tremendous importance of the social environment on the developing organism must not be forgotten and it is concluded that neural limits may be set by genetic and environmental factors, and in any given patient ancestral transmission, early physical trauma and social trauma may each play a part.

Gottlieb, J. S., Knott, J. R., and Ashby, M. C. (1945) *Arch. Neurol. Psychiat.*, Chicago, 53, 138.

CHOLERA

See also B E M P, Vol III, p 166, and Cumulative Supplement, Key No 235.

Epidemiology*Epidemic spread of cholera in India*

Effect of rainfall, humidity and pilgrimages—A paper read by Rogers before the Royal Society of Tropical Medicine and Hygiene deals with the relation of cholera incidence in India to the three factors rainfall, absolute humidity and pilgrimages. It is a well-known fact that cholera dies out or greatly declines during the winter months in most of the provinces of India. The exceptions are those provinces in which absolute humidity—a measure of combined temperature and humidity—does not fall below 0.400 in January. It has been shown that the rate of cholera incidence rises with the seasonal rise of absolute humidity to over 0.400 which occurs in various provinces at different times of year. Endemic areas are those in which absolute humidity never falls appreciably below 0.400. Rainfall also appears to be related to cholera incidence. In 40 out of 41 epidemics studied, the monsoon rains of the previous year were found to have been deficient in the districts affected. The one exception, an epidemic which occurred in 1894, was explained by the fact that 3,000,000 pilgrims attended the 12-yearly Khumbh Fair at Allahabad in that year, and were responsible for spreading the disease. The factor of pilgrimages is one of great importance in relation to cholera. Epidemics have occurred after large fairs regularly in all the years for which data

are available. The rate of spread of the disease is proportional to the rapidity of communications. From an analysis of the cholera incidence for each decade 1880–1939 the author concludes that a watch on the south-west monsoon rains between June and October enables a high rate of cholera incidence in the endemic areas to be predicted several months before the spread of epidemics from the endemic to the epidemic regions. The risk of cholera being spread by pilgrims returning from a particular fair can also be foreseen by knowledge of the climatic data and of the presence of cholera in regions through which the pilgrims have to travel. The only practical method of limiting the spread of cholera by pilgrims is by immunizing them against the disease, preferably before they reach the fairs. The results of compulsory inoculation are shown in the case of the Pandharpur fair. The fair had proved to be so dangerous that from 1936 pilgrims were forbidden to attend the fair unless they had been immunized within the preceding 3 months. An outbreak of cholera did not occur in any of the subsequent 6 years.

Bacteriology

The cholera vibrio

Serological types.—Tang, Chu and Wong investigated *Vibrio comma* isolated from the 1942 Kunming epidemic with special reference to serological types. One hundred and twenty-nine rectal specimens were collected from 110 cases of clinical cholera, from which 83 strains of vibrio (including two inagglutinable strains) were obtained. Specimens from 12 normal persons, 8 cases of diarrhoea or dysentery and 1 of undiagnosed coma were negative. From 2 of 5 specimens of water from wells in infected areas two strains of inagglutinable vibrios were obtained. Young agar slant cultures were studied microscopically for motility, agglutination against stock serum, morphology and Gram staining reactions. Suggestive representative cultures were kept in Hitchen's semi-solid medium for further investigation. Identification was then pursued by gelatin liquefaction, cholera-red reaction, carbohydrate fermentation and their effect on erythrocytes (Greig's technique). Cultural studies and serological investigation revealed two distinct types of cholera vibrio in the one epidemic. During a period of several months the Inaba type alone was found in all the cases studied but towards the end of the epidemic Inaba and Ogawa types were encountered together. Since natural transformation from one type to another is at present non-proven, the authors reject the idea that during passage through the patients the Inaba type assumed the Ogawa form. The authors think that the significance of serological types should not be exaggerated, although they are useful in tracing the source and observing the progress of an epidemic. Owing to uncertainty of cross immunization Tang, Chu and Wong advise inclusion of both types in the preparation of cholera vaccine.

Rogers, L. (1944) *Trans. R. Soc. trop. Med. Hyg.*, 38, 73.

Tang, F. F., Chu, C. M., and Wong, Y. W. (1944) *Indian J. med. Res.*, 32, 1.

CLIMACTERIC AND ITS DISORDERS

See also B.E.M.P., Vol. III, p. 228; and Cumulative Supplement, Key Nos. 242 and 243.

The question of a climacteric in the male

Diagnosis

A rare syndrome.—Clinical observation suggests that a true climacteric in the male is a rare syndrome. Heller and Myers consider that testicular failure may be held to exist (1) by the evidence of elevation in gonadotrophic excretion in the urine, comparable qualitatively with that occurring in castrated males, (2) by histological signs of testicular atrophy or degeneration at testicular biopsy, and (3) by the restoration of potency by substitution therapy with androgens and the reappearance of symptoms on their withdrawal. By these standards the authors established a diagnosis of male climacteric in 23 cases. Vasomotor, psychic and constitutional symptoms were identical with those of the female menopause. There was a significant tendency for loss of sexual potency, hot flushes and nervousness to appear concurrently and the patient generally could tell the month or season when the symptoms started. Urinary symptoms took the form of decreased force or size of stream, frequency and hesitancy. Psychogenic impotence imitates this symptomatology closely but in this case the symptoms are usually found to have been present throughout adult life or to have occurred abruptly after psychic trauma. The absolute differentiation from the male climacteric, however, rests on the finding in the psychogenic group of normal amounts of urinary gonadotrophins. Satisfactory treatment of the male climacteric is afforded by intramuscular injections of testosterone propionate and by implantation of testosterone pellets, but not by the oral or sublingual administration of methyl testosterone. Since this treatment will not affect symptoms of psychogenic origin, it can be used too as a simple therapeutic test in order to differentiate them from those of climacteric origin by giving testosterone propionate in 25-milligram doses 5 days a week for 2 weeks and studying its effect. Heller and Myers conclude that, although the male climacteric may occur as early as the third decade, it is a relatively rare syndrome affecting probably only a small proportion of men who live into old age.

Symptoms

Clinical picture and treatment.—Werner states that there is absolutely no basis for the belief that man does not have a decrease in sex function in later life or that he cannot have a climacteric. If there is hypofunction of the gonads a glandular-autonomic imbalance develops which occurs commonly between the ages of 45 and 55 years. The manifestations of the male climacteric are nervous, circulatory and general. The chief nervous symptoms are a feeling

of tension, aggravated by excitement or fatigue, restlessness and poor sleeping, numbness and tingling of extremities and formication. Headaches, especially of the vertex and occipito-cervical region, are of almost specific diagnostic importance in gonadal hypofunction. Mental symptoms include failure of concentration and memory, depression or mild melancholia and loss of self confidence, all of which when severe constitute involutional melancholia. Circulatory disturbances consist of capillary flushing, often associated with perspiration, vertigo, tinnitus and scotomata, tachycardia and dyspnoea the two latter often occurring at rest. Werner presents a study of 54 patients with these symptoms which in the absence of cardiovascular disease or hypothyroidism he attributes to the climacteric syndrome. The study included cases of cryptorchidism, castration and hypogonadism but 44 patients were classified as being in the male climacteric without demonstrable testicular lesions. Thirty eight patients had an average basal metabolic rate of -17 per cent but no evidence of hypothyroidism. Decrease or loss of potency was admitted by 90 per cent of the patients. Testosterone propionate, by intramuscular injection of 25 milligrams 3 times a week for 2-3 months, was effective in relieving the symptoms. Werner states that testosterone should not be given solely for the purpose of stimulating potency. Apart from androgens, the oestrogens have also an important role in therapy especially if the prostate is large or is giving symptoms.

Heller, C G, and Myers G B (1944) *J Amer med Ass*, 126, 472
Werner, A A (1945) *J Amer med Ass*, 127, 705

CLIMATE IN THE TREATMENT OF DISEASE

See also B E M P Vol III, p 235

Meteorological factors

Effects on the body

Barometric and blood pressures—Ray discusses the effect of certain climatic factors on bodily health. He describes some of the physiological mechanisms by which a constant internal environment is maintained in the face of changing climatic conditions. In the maintenance of an equable body temperature constant stimulation of the skin is necessary. People with inefficient sympathetic-adrenal functions are readily recognized types, they suffer from colds, asthma, lumbago and sciatica and have harsh dry skins which do not sweat readily. For elderly people whose recuperative powers are diminished life in a warm equable climate is beneficial. As the rate of cooling of the body depends upon surface evaporation, a wind may have a profound effect upon the body exposed to it although the physical nature of the air is unaltered by it. Thus cooling of the body will result from a wind if the air is at a temperature below that of the body and also if the wind is warm but dry. In normal health such loss of temperature is stimulating and conducive to health. Petersen has shown by comparative records of normal people that a rise of barometric pressure or the beginning of a fall after these peaks. In normal people this rhythm is harmless and may be shown only by a change of mood. In the spring when there are frequent changes of barometric depression, the blood pressure will often show repeated sharp peaks and periods of lowering of the diastolic pressure. On elderly and feeble persons whose adaptive powers are depressed these changes in atmospheric conditions may have adverse effects.

Ray, M R (1944) *Brit J phys Med NS*, 7, 130

COELIAC DISEASE

See also B E M P, Vol III, p 262, and Cumulative Supplement, Key No 247

Clinical picture

Stools

Evaluation of fat—Andersen describes methods of evaluation of fat in faeces especially in the coeliac syndrome. Even during starvation fat is normally present in faeces. Steatorrhoea occurs in infants and children suffering from chronic indigestion and especially in those presenting the coeliac syndrome. It must be borne in mind that in the latter condition the stools may be foul and foamy, without any relative excess of fat and that the excessively fatty stools of the patient with pancreatic deficiency may appear to be normal. Naked eye investigation is therefore unreliable and faecal fat must be quantitatively determined with adequate controls of diet and control determinations for comparable subjects. The dry and wet weights of stools and the total fat and neutral and fatty acid fractions, respectively, of the daily faecal excretions of normal infants and children on ordinary diets were investigated and the writer states that they showed interesting variations with age. At the age of 2-6 months the stools examined showed a smaller total quantity with relatively greater fat and a smaller proportion of neutral fat. The value of the microscopical examination of faeces for fat, staining with sudan IV, was investigated and was found to be reliable for eliminating patients without steatorrhoea. The author concludes that a single determination of total fat in faeces by the Sperry method, using 10 drops of concentrated sulphuric acid is more reliable than is a single determination by the Fowweather method and about equal to the mean of duplicate determinations by it. The smaller quantity of materials required for the Fowweather method renders feasible duplicate determinations, which it is often impossible to obtain by the Sperry method. The latter method involves less labour. As neutral fat is hydrolysed *in vitro*, at temperatures as low as $6-7^{\circ}\text{C}$, faeces may show no relative excess of fat. In patients with good absorption there may be a great deal of neutral fat, including the unsaponifiable fraction, and in those with steatorrhoea there may be very little.

Diagnosis

Differential diagnosis

Analysis of duodenal drainage.—Philipsborn, Lawrence, Gibson and Greengard have reached the conclusion that quantitative analysis of the duodenal drainage for enzymatic activity and notation of the volumetric response of the pancreas to secretin or to intraduodenal N/10 hydrochloric acid, are more reliable laboratory aids in the differential diagnosis of fibrocystic and coeliac diseases than are those provided by stool examinations and vitamin A curve estimations. The authors' methods of obtaining duodenal secretion and of measuring its tryptic, amylolytic and lipolytic activities are fully described. The fasting values obtained by analysis of the duodenal drainage of normal children in this series closely resembled the results obtained by Klumpp and Neale. An estimate for tryptic activity is the most reliable index of pancreatic function, since it varies less with age than does pancreatic amylolytic activity and is more accurately determinable than is lipolytic activity. In children, values of less than 4 grammes of nitrogen, liberated from a casein substrate per 100 cubic centimetres of duodenal fluid, are abnormal. Pancreatic amylase is deficient if, during the first year of life, less than 0.5 gramme of dextrose is liberated from starch, digested by 100 cubic centimetres of duodenal contents for a given period of time, or if, after one year of age, less than 2 grammes of dextrose is liberated. Pancreatic lipase was considered to be deficient when, by the authors' admittedly crude technique, less than 60 cubic centimetres of N/20 sodium hydroxide was required to neutralize free fatty acids liberated per 100 cubic centimetres of duodenal drainage. Duodenal secretions from children with fibrocystic disease and from those with coeliac disease showed, respectively, very low or absent and normal enzyme concentrations. Transient pancreatic insufficiency apparently accounted for some feeding problems in children studied. Pancreatic stimulation by intravenous secretin or intraduodenal N/10 hydrochloric acid caused significant increase in the volume of duodenal juice obtained from normal children and from those with coeliac disease. Children with fibrocystic disease which pathologically is characterized by an intrapancreatic block, showed no significant pancreatic response after similar stimulation. A significant pancreatic response may, however, be given in cases of non-specific achylia or hypochylia of the pancreas.

Treatment

Diet

Proteolysed beef.—Adamson and Lewes recommend proteolysed beef as a useful adjunct in the treatment of coeliac disease. In the earliest years of life the protein requirements per unit of body weight are about twice those of an adult, but the ability to digest protein foods is proportionately lower. In coeliac disease this impairment of the powers of absorption, especially of fat and protein, is greatly increased. It was suggested, therefore, that a high protein intake might be ensured by the oral administration of proteolysed beef. It is prepared by heating a mixture of 6 pounds of minced lean beef, 15 grammes of papain and 100 ounces of water in a steam-pan, and maintaining the heat at 60° C. for 3 hours. The mixture is then heated to 100° C. and is boiled for 10 minutes. Residual fat is removed by straining, and the volume is adjusted to 6 fluid pints with water. A pint of the mixture, equal to one pound of beef, is given daily. In one of two well defined cases of the disease the patient, a child, was treated for many months by routine remedies which included vitamins, ascorbic acid and calcium. Some slow improvement took place, but it was negated by a series of intercurrent affections, including Sonne dysentery. Eventually the patient was put on proteolysed beef therapy and parenteral vitamins were gradually discontinued. Within 9 months there was no doubt that the child was well on the way to recovery. In the other case proteolysed beef was given with routine treatment from the start, and within a comparatively short time there was a noticeable improvement.

Vitamin supplements.—Paterson, Pierce and Peck report on experiences in the Hospital for Sick Children, Great Ormond Street, London, of the treatment of coeliac disease during 1943 and 1944 with a regimen similar to that advised by May and his colleagues, who advocated a normal balanced diet supplemented by vitamins A, C and D and the parenteral administration of crude liver extract and vitamin B complex. Of the 30 cases so treated, 13 were patients with typical symptoms and history of idiopathic coeliac diseases confirmed by full pathological investigations; 13 cases presented typical symptoms, signs and course and characteristic stools, but wartime limitations prevented full pathological confirmatory investigations; 4 cases were classified as coeliac syndromes since a focus of infection was found. A normal balanced diet throughout treatment was the goal; in severe cases this was found to be impracticable and a lowfat diet was given, but after about 3 or 4 weeks of treatment it was found to be possible to introduce fats. Proethron Forte (2 cubic centimetres) was given intramuscularly 2 or 3 times a week. The vitamin B preparations used were Lederle's B complex and Beminal given intramuscularly, and B-Plex administered orally. Improvement in weight and height and in general health were obtained in the early weeks of treatment and were sustained in both of the first two groups. Similarly the 4 cases of coeliac syndromes showed improvement. Oral glucose tolerance curves were recorded before and after treatment in 9 cases; prior to treatment the curves were below 40 milligrams per cent, which figure was regarded as the normal low limit. After treatment, in 2 cases the peak rise was found to be over 40 milligrams per cent, and there was improvement in 7 others. Vitamin A absorption curves were obtained in 5 cases before and after treatment; in no case did it return to the

normal, but there was improvement in 3 cases. In 4 cases stools with large fat content persisted in spite of general improvement and therapy and the authors comment that as the defect in fat absorption was not improved in these cases, an irreversible change perhaps had taken place which could not be corrected by this therapy.

Adamson, A. C., and Lewes, D. (1944) *Brit med J*, 2, 370

Andersen Dorothy H. (1945) *Amer J Dis Child*, 69, 141

Paterson, D., Pierce, Mila, and Peck, Eleanor (1944) *Arch Dis Childh*, 19, 99

Philpsborn, H. F., Lawrence Grace, Gibson, S., and Greengard, H. (1945) *J Pediat*, 28, 107

COLDS

See also B E M P, Vol III, p 271

Preventive measures

Drugs

Disappointing results with sulphanilamide lozenges—Hayden and Bigger describe the use of lozenges containing 0.065 gramme of sulphanilamide in the prophylaxis of infections of the respiratory tract. The lozenges were distributed to 1,108 recruits, and each man took 1 lozenge 5 times daily for 16 days. The men were instructed to make the lozenges last as long as possible in the mouth and to swallow their saliva during this procedure. The method produced a concentration of 300 milligrams of sulphanilamide per 100 cubic centimetres of saliva. A considerable local action might have been expected, therefore, but it is improbable that the dose swallowed in 24 hours could have had any general action. A comparison was made between these results and those obtained in a group of 1,165 recruits taking lozenges which did not contain sulphanilamide. The statistics relating to the first group indicated a reduction in the incidence of severe coughs and of fresh or increasing common colds. On the other hand, comparison with the second group showed that there was an increase in the number of slight coughs in the men taking sulphanilamide. It is concluded that, apart from the slight risk involved, the sulphanilamide lozenge method of prophylaxis is not worth the trouble and expense.

Treatment

General management

Layton views the management of the common cold with the knowing eye of one who has seen many fashions in treatment come and go. In search of truth he takes his reader into his grandfather's consulting room, his mother's kitchen, a factory lavatory and Mr. Middleton's broadcasting studio. Truly, as he says, in the treatment of the common cold science has done nothing and empiricism is the order of the day. Once the possibility of influenza has been discounted, Layton does not believe it to be necessary for a healthy person with a common cold to knock off duty. He pleads for the conservation of the lymph tissue of a child's throat as the first line of defence against infection. Removal of tonsils is not a cure for recurrent colds. At the onset of a cold a purgative should be given, preferably castor oil to the healthy young adult and Gregory's powder to the child, with the object of emptying the alimentary canal from duodenum to rectum. Excessive amounts of aspirin may leave the patient in a worse state than would any common cold. For the purpose of "cutting the phlegm", Layton believes that the best drug is bicarbonate of soda. Management is based on the patient rather than on the disease. Adequate food, rest, exercise and ventilation are all important and the physician should feel responsible for the care of the patient in every detail of his life both in treatment and prevention. With regard to the latter, Layton recalls the fads and fancies of growing a beard, wearing spats, taking snuff and using tobacco as preventives. Vaccines, although irrational in the light of aetiology, appear to give good results with some patients and in the hands of some doctors. The general impression received is that anything may succeed provided it is done well enough and is believed in.

Hayden, A. F., and Bigger J. W. (1945) *Brit med J*, 1, 81

Layton, T. B. (1945) *Practitioner*, 154, 65

See also B E M P, Vol III, p 292

Ulcerative colitis

Treatment

Surgical aspects—Corbett, quoting the dicta "once an ileostomy always an ileostomy" and "an ileostomy is the price that some patients must pay for life", reviews the surgical treatment of chronic ulcerative colitis. Only 4 years ago the most usual operation performed on sufferers from the complaint was appendicectomy. The aetiology of the disease is obscure. Bacterium *streptococcus*, which is normally present in the bowel and is found in diarrhoea of other causation, is not agreed, by observers in Great Britain, to be a specific cause of ulcerative colitis, emotional factors are undoubtedly important. Persistent and patient medical treatment must always precede the consideration of surgical intervention, the milder cases respond well to conservative measures. Surgical treatment has ultimately to be applied in about 15 per cent of cases in which, despite adequate medical treatment, the condition persists. In such cases the disease may even endanger life, or at any rate may frequently recur, or it may be associated with complications, or certain patients (never children) may have a severe fulminating type of the disease. In all these cases surgical treatment is indicated. The essential

COLITIS

to be aimed at in operative treatment is absolute rest for the colon which appendicostomy fails to afford. It further does not always provide a satisfactory entrance for irrigating fluids and may involve constant leakage even with a catheter and spigot *in situ*. If the entrance closes, the colonic condition may recur; its presence is inconvenient in event of need for subsequent surgical procedures; peritonitis may arise from the appendix stump in course of irrigation. The mortality during the last 10 years has been about 20 per cent. Caecostomy has much the same disadvantages and the author doubts whether irrigation, the object of both appendicostomy and caecostomy, has any better effect than has rest alone. Colostomy puts the diseased portion at rest and allows functional activity of the proximal colon and is indicated in regional colitis, in which temporary colostomy should precede local resection. Ileosigmoidostomy has proved on the whole to be dangerous and uncertain in its results which depend upon the condition of the sigmoid and rectal wall. The author advocates the performance of ileostomy, and then, if this alone fails to cure or if complications occur, an ensuing colectomy.

Corbett, R. S. (1945) *Proc. R. Soc. Med.*, 38, 277.

CONCUSSION AND COMPRESSION

See also B.E.M.P., Vol. III, p. 355; and Cumulative Supplement, Key No. 255.

Aetiology of head injury

Cerebrospinal fluid

Escape from nose or ear.—Dandy gives an account of those conditions caused by trauma, tumour or operative procedure in which the cerebrospinal fluid escapes from the nose or the ear. Two of his cases were associated with air in the cranial chamber and the ruptures in the dura and the bone were not superimposed, air finding its way in and being unable to get out. Both patients were comatose on admission to hospital and both recovered. The fluid escapes through a fistula which, if closed, will cure the condition. Cerebrospinal fistulae are a potential source of meningitis or cerebral abscess; many heal spontaneously. If a fistula with undiminishing flow continues for more than 2 weeks, operative attempt at closure should be made. The only danger is when cerebral infection precedes the operation. The site of the fistula must be determined as accurately as possible; a depressed cranial fracture may indicate its position. If it results from operative procedure, the site will be in the tract of the operation. The frontal, ethmoidal and sphenoidal sinuses require x-ray examination. The dural aperture when found should be sutured over with autogenous grafts of fascia lata. If the dura is too thin to suture, strips of fascia can be laid over the opening and treated with 3.5 per cent solution of iodine for the purpose of promoting adhesions. The opening in the bone may be closed with bone wax. This is not essential in cases in which the dural opening is well sutured over fascial reinforcement. In some operative procedures it is not easy to avoid opening the frontal sinus. In other cases tumours have already invaded it. Escape of fluid into the middle ear, if not traumatic, is due to piercing of the mastoid bone and the dura by the operator. This usually happens in the roof of the petrous portion of the temporal bone. Eight of 11 patients reported on are permanently cured.

Treatment

Of complications

Psychiatric investigations and treatment.—Denny-Brown analyses a group of 200 cases of closed head injury. The series of patients comprised 125 males and 75 females. Patients under the age of 15 years and over the age of 55 were omitted from the series in order to minimize the influence of age and to concentrate on groups in regular employment. Vagrants and chronic alcoholic addicts were also excluded. The patients were examined by a team of investigators including neurologists, psychiatrists, a psychometrist and a social worker. The chief factors of prognostic ill omen were those indicative of injury to the brain and those relating to the environment. Only 16 patients complained of persistent symptoms which were directly referable to structural physical disorders. During convalescence the most common combination of disabilities consisted of headache, dizziness, and mental symptoms such as anxiety, fatigue, depression and change in personality. The influence of occupation on the duration of disability is probably related to the question of compensation as well as to age and to type of injury, since civil servants (e.g. policemen and firemen) and labourers were away from work longer than were students or domestic workers. Patients with a past history of neurosis or psychopathic personality returned to work earlier than did those judged to be normal. This was an unexpected finding. Furthermore, a family history of psychiatric disorder was without significance. An increase in disability occurred in patients with fracture of the skull, prolongation of disorientation beyond 24 hours, and affective states such as restlessness and apathy and those inducing emotional outbursts. The presence of extensor plantar responses and increased tendon jerks, with or without corresponding asymmetry of the abdominal reflexes, was also associated with delayed recovery. Persistent intellectual defect residual to prolonged disorientation occurred in only 2 patients. It is doubtful whether trauma alone can induce persistent dementia in a healthy brain. Mental symptoms of any kind occurring during convalescence were very closely correlated with prolonged disability. Psychiatric treatment should prove to be of value in modifying the severity of these manifestations. The expression, post-concussion syndrome, comprises headache, dizziness and mental symptoms; the author considers that the term should not be used, since the full syndrome

only slightly exceeded the correlations of any of the symptoms occurring singly or in other combination with the same factors

Dandy, W E (1944) *Arch Surg, Chicago*, 49, 75

Denny-Brown D (1945) *J Amer med Ass*, 127, 429

CONJUNCTIVA, INJURIES AND DISEASES

See also B E M P, Vol III, p 365, and Cumulative Supplement, Key No 256

Injuries

Chemical injuries

Snake venom ophthalmia—Ridley discusses snake venom ophthalmia, giving a clinical example *Naja nigricollis*, the black necked cobra, can spit jets of venom into its victim's eyes, and other cobras have the same power to a less extent Snake venom causes great irritation in the eyes but conjunctival absorption is slight and if early treatment is given sight usually recovers, although blindness from corneal opacities has been reported In Ridley's example venom had entered the patient's right eye only He received prompt medical attention, when moderate conjunctival injection, oedema and opacity of the lower two thirds of the cornea and loss of corneal sensation were found Saline irrigations and atropine were given, but no antivenene The next day there was chemosis with stripping of the corneal epithelium Corneal sensation did not return for 9 days Slow regeneration of loosely attached corneal epithelium occurred until after 14 days, the cornea was normal apart from a localized faint opacity, vision being 6/6 Ridley comments on the prolonged corneal anaesthesia and after describing the nature and therapeutic uses of snake venom, suggests that it might be used to procure prolonged anaesthesia in the treatment of painful conditions of the anterior segment of the eye

Inflammation due to bacterial infection

Ophthalmia neonatorum

Penicillin treatment—Sievers, Knott and Soloway give the results of treatment by penicillin in 8 cases of ophthalmia neonatorum A limited supply of the drug was made available for this particular purpose since, although benefit had resulted in this condition from the use of sulphonamides, it was found that many patients were intolerant of or quickly became resistant to them All 8 patients received instillations of 0.5 per cent atropine sulphate and irrigations of sterile water during the acute stage As there was not a precedent for dosage, it was prejudged at 10,000 units given intramuscularly every 3 hours for a total of 6 injections In practice this was found to be inadequate, and the amount given was adjusted to each individual case In 6 patients there was subsidence of acute inflammation within 24 hours with progress to complete recovery in from 3 to 6 days In 7 of the cases the aetiological agent was found to be *Neisseria gonorrhoeae* In 5 its presence was confirmed by fermentation tests, but in 2 sub-cultures could not be obtained for this purpose No definite cause of infection could be found in one case This was one of the two patients who failed to respond to penicillin The other gave what were considered to be positive skin reactions to the drug, following each other in the order of papular, vesicular and urticarial eruptions as the dosage increased After a comparatively long time both these cases eventually responded to administration of sulphonamides Smears and cultures were made at the inception of therapy, again at the time of the third injection, and at intervals until bacteriological examination gave 3 consecutive negative findings specifically The causal organism was noted to be absent in from 9 to 24 hours in all patients who responded to the use of penicillin, except in the case of one from whom a final positive culture was obtained on the third day

Ridley, H (1944) *Brit J Ophthalmol*, 28, 568

Sievers, J J, Knott, L W, and Soloway, H M (1944) *J Amer med Ass*, 125, 690

CONSTIPATION

See also B E M P, Vol III, p 376, and Cumulative Supplement, Key No 257

Pathogenesis

Colonic constipation

Mechanism of the colon in health and dysfunction—Hardy discusses the activities of the large bowel and the disorders which depend upon disturbance of function In a series of healthy medical students radiographic studies showed that the process of colon filling is haphazard and that there are extreme variations in haustral formation The clefts and haustra subserve the functions of mixing the bowel contents and are the results of active contraction of the circular muscle coat The movements of the colon consist of a slow and irregular diastolic filling, interrupted two or three times a day by a very rapid and powerful systole It appears that the distal colon and the rectum are more intimately under the control of the central nervous system than are other parts Stimulation of the sacral division of the autonomic system results in contraction of the bowel with relaxation of the anal sphincter, increased vascularity and the secretion of mucus The colon may be capable of much self injury by overaction, by exhaustion and by expulsion of the protecting mucus Habitual constipation is colon disorder in its simplest form In most cases it is due to dyschezia and faulty training One bowel action a day is often regarded as the only normal condition, but a questionnaire addressed to 440 nurses showed that 9 per cent of them had their bowels opened less than once daily, whereas in 32 per cent of cases defaecation occurred more than once a day

Perfection of function is more important than regularity. A primary exaggeration of normal function occurs in colon neurosis, which is essentially a disease of sedentary workers. Ill-judged purgation is a characteristic accompaniment of the disorder. In the aetiology of colon neurosis emotional and temperamental considerations are of more importance than are reflex disturbances and humoral mechanisms. The author noted some form of nervous instability in 135 out of 218 patients. The manifestations of colon neurosis include abdominal pain and distension, reflex dyspepsia, and irregular defaecation. Mucous colitis was a common variant of the disorder until 1914, when it disappeared with remarkable suddenness. Psychological maladjustments may occur in ulcerative colitis. Emotional stresses were found to be important factors in 40 of 68 patients with this disease. Contrary to the findings of some American authorities allergy does not play an important part in determining the colonic reactions in ulcerative colitis. The disorder remains obscure in its aetiology, uncertain in its course and fickle in its response to treatment.

Treatment

Chronic constipation

Defects in intestinal mechanism.—Soper, writing on chronic constipation, points out that the gastro-intestinal tract may be regarded as a mechanism the motor apparatus of which functions in a rhythmic way and is concomitant with specific chemical changes. In the living person the anatomical relation of different portions of the colon are not constant and vary with the structure and bodily build of the individual. In the hypersthenic the stomach is transverse and relatively high, the sigmoid loop or pelvic colon is high above the pelvic cavity and the rectal ampulla is small with an anal canal of about 2½ inches in length. In the asthenic the stomach is long, narrow and fish-hook formed and extends down into the pelvis. Part of the transverse colon is massed together with the pelvic colon in the pelvic cavity and the rectal ampulla is capacious with a relatively short anal canal. These positions should be regarded as anatomical and not pathological. The rectosigmoid apparatus is an important factor. It consists of the terminal 2 inches of the pelvic colon and proximal 1½ inches of the rectum. Its nerve supply is from sympathetic ganglia formed from lumbar and sacral spinal nerves which cause intestinal contraction. The tonicity of the rectosigmoid apparatus keeps the rectum empty of faeces except during the act of defaecation. Modifications in colonic motility occur in accordance with either the asthenic or hypersthenic habitus of the individual. As regards treatment, enemas and purgatives should be stopped, thereby allowing the faecal column to be formed in the lower colon. A pint of cold water should be taken on rising, followed by exercises involving the abdominal muscles. Strong intermittent pressure with the hands over the left side of the abdomen is particularly recommended while defaecation is taking place. Spastic conditions of the colon often respond to oil retention enemas, which are conveyed to the caecum by reverse peristalsis. The author has had much success by this means in cases of ulcerative colitis and of tuberculosis of the rectum and lower colon.

Laxatives

Effect of phenolphthalein.—McGuigan, Steigmann and Dyniewicz, believing that pharmacopoeial doses of certain laxatives are unequal to their task, demonstrate that larger—but not too large—doses have the optimum effect. Groups of normal individuals, groups with constipation of recent origin and groups with chronic constipation were treated at certain intervals with several laxatives in varying dosage. The laxative chiefly studied was white phenolphthalein, the pharmacopoeial dose being 0.06 gramme. This dose has a laxative effect in only 48 per cent of normal individuals; 0.1 gramme has a similar effect in 63 per cent, 0.2 gramme in 74 per cent and 0.3 gramme in 88 per cent. In a normal group, 0.06 gramme of yellow phenolphthalein gives a laxative effect in 73 per cent. It appears that the white pharmacopoeial preparation has been purified of its yellow phenolphthalein content and is rendered less potent. Patients with constipation of recent origin give nearly similar percentages with increasing doses. It is pointed out that phenolphthalein is only slightly soluble in water. A dose of 0.1 gramme in alcoholic elixir has a laxative effect in 80 per cent of both normal and chronically constipated individuals. A pharmacopoeial dose of a laxative should have an effect in over 50 per cent of cases. This is obtained in normal subjects when the dose is doubled. Treble the dose is needed for constipated patients and for some even larger doses. The authors apply the same criticism to the pharmacopoeial dose of aromatic fluid extract of cascara sagrada, double the dose having been found to be the optimal.

Hardy, T. L. (1945) *Lancet*, 1, 519, 553.

McGuigan, H. A., Steigmann, F., and Dyniewicz, J. M. (1944) *Amer. J. digest.*

Dis., 11, 284.

Soper, H. W. (1944) *Amer. J. digest. Dis.*, 11, 255.

CORNEA, INJURIES AND DISEASES

See also B.E.M.P., Vol. III, p. 424; and Cumulative Supplement, Key No. 260.

Injuries

Treatment

Comparison of local and general application of penicillin.—In order to estimate the relative efficiency of local and of general administration of penicillin on corneal ulcers induced by a Gram negative bacillus cultured from the culs-de-sac of rabbit eyes, experiments have been carried out on rabbits by Leopold, Holmes and LaMotte. A standard lesion, capable of variation, is arrived at by the injection into the cornea of a known number of the irritant

bacilli, the progress of the inflammatory reaction being noted daily. Fifteen blue-eyed chinchilla rabbits were used in each of two experiments. In the first, 400 organisms were injected into the corneae of all rabbits. After 2 hours, the right eye of 12 rabbits received local penicillin treatment, left eyes did not receive any treatment. Three of the rabbits, after 2 hours, received penicillin administered intramuscularly without local treatment. All untreated eyes and each of the 6 eyes intramuscularly treated followed the course of the standard lesion. The locally treated eyes showed hardly any reaction. In the second experiment, 10,000 organisms took the place of the 400 and treatment was delayed for 24 hours; the technique being identical with that of the first experiment. In all eyes, treated or untreated, inflammation developed, pronounced lesions being present after 72 hours. After that period the locally treated eyes showed a smaller area of infiltration and in 6 of them hypopyon did not develop. These continued to improve, whereas 10 of the untreated eyes perforated after 4 weeks. In 2 eyes the process of inflammation subsided. The comment is made that the intramuscular injection of penicillin has not any curative influence on already established corneal ulceration.

Experiments with penicillin and sulphonamides—Smelser and Ozanics studied the effects of penicillin and of various sulphonamides on the rate of cell division in and the healing of corneal burns and abrasions in rats. They sought a chemotherapeutic agent which would not interfere with reproduction of healthy epithelial cells or with their migration over denuded areas produced by injury. One eye of the animal was treated and the other served as control. It was found that in 12–18 hours corneal abrasions healed without marked increase of mitotic figures and that thermal burns became covered with epithelium within the same length of time but showed a large increase in mitotic figures during the process. The sulphonamides were applied hourly as fine powders or 5 per cent ointments and penicillin also hourly in aqueous solution at a hydrogen ion concentration of 6.5–7.0 containing 500 Oxford units per cubic centimetre. Cell migration was more inhibited by sulphacetamide than by sulphadiazine powders but there was no evidence that sulphacetamide powder inhibited cell division; therefore, as in the case of the untreated injuries, the number of mitotic figures bore no direct relation to the extent to which or the speed with which the defects in the cornea were covered. Sulphonamide ointments inhibited cell migration slightly less than did the powders. If the therapeutic effects are assumed to be similar, sulphadiazine and penicillin are preferable since they inhibit cell migration less than do sulphathiazole and sulphacetamide, and ointments are apparently more effective than are powders. Sulphadiazine tended to increase cell division and sulphathiazole to depress mitosis. Bellius had previously shown that epithelialization was inhibited by administration of sulphonamides. Berens also noted that a sulphonamide ointment delayed healing of abrasions. The authors' investigations showed that healing proceeded most rapidly in the untreated injuries.

Ulcers

Treatment

According to cause—Evans reviews the modern treatment of corneal ulcer both in general terms and in relation to the various aetiological factors concerned. The first consideration of treatment is rest, and this is most easily achieved by application of a firm bandage. Only drops or ointment also help to prevent damage to the healing epithelium and in many cases cocaine, 0.5–1 per cent, is of great relief and is quite safe when the lids can be shut and the general corneal tissue is healthy. Atropine is always indicated when circumcorneal infection is marked or when associated iritis is shown by the presence of posterior synechiae. Neurotrophic and anaesthetic ulcers are prone to break down and prolonged protection may need to be given by the performance of tarsorrhaphy or the wearing of goggles. Primary Phlyctenular keratitis in children calls for attention to diet, the giving of cod liver oil and malt, the removal of nearby septic foci and a course of tuberculin injections in those cases with a strongly positive Mantoux reaction. Residual nebulae are treated by mydriasis, optical iridectomy or corneal grafting. In all cases early diagnosis is essential and is confirmed by staining with a drop of 2 per cent fluorescein gently washed out with a few drops of physiological saline. Thereafter, treatment should be firmly carried through. The policies of wait and see, and hope are not, according to Evans, of any help in cases of ulcer. When home treatment is inefficient, early transfer of the patient to hospital is always amply repaid by results.

Evans, P. J. (1945) *Med. Pr.* 213, 100.

Leopold, I. H., Holmes, Lida I., and LaMotte, W. O., Jun. (1944) *Arch. Ophthal.* 31, 32, 193.

Smelser, G. K., and Ozanics, V. (1944) *Amer. J. Ophthal.* 27, 1063.

CRANIAL NERVE AFFECTIONS

See also B.E.M.P., Vol. III, p. 470.

The eighth nerve

The cochlear division

Review of tinnitus aurium—Atkinson discusses the nature and control of tinnitus aurium. He states that tinnitus can be considered as the homologue of paraesthesia in the peripheral sensory apparatus. The cause of peripheral neuritis is thought by many to be on a vascular basis at least in part, and working on the above analogy the author describes the effect of

altering the blood supply to the cochlea. Owing to the inaccessibility of the region, the use of general vasodilator and vasoconstrictor drugs and the procedure of blocking the stellate ganglion are the only possible methods of treatment. In the experiments described, all patients had had longstanding and persistent tinnitus; all were tested with histamine intradermally. In 18 the stellate ganglion was blocked by infiltration of 1 per cent solution of Novocain (procaine hydrochloride); the results were that in 6 there was no change, in 2 the condition became worse and in 10 there was distinct improvement in symptoms lasting from 2 to 72 hours. Vasoconstrictor drugs produced a striking and consistently bad effect upon the tinnitus. A single injection of a vasodilator drug did not have a noteworthy effect, but acetylcholine gave the best results. Atkinson considers that the above observations suggest that the symptom of tinnitus is caused by vascular disturbances. He reports that the treatment with nicotinic acid of 175 cases of tinnitus—including 106 cases of Ménière's syndrome—caused relief and improvement in 63 per cent of cases, the greatest percentage improvement (85 per cent of 47 cases) being in cases of conductive deafness with tinnitus.

Atkinson, M. (1944) *Ann. Otol., etc., St. Louis*, 53, 742.

CROHN'S DISEASE

See also B.E.M.P., Vol. III, p. 508; and Cumulative Supplement, Key No. 277.

Morbid anatomy

Histology

Review of micropathology.—Schepers reviews the literature on regional ileitis as a clinico-pathological entity and presents a detailed consideration of its micropathology. Primarily, the submucosa and serosal adventitia are simultaneously involved. The main reactions affect the submucosa which shows massive interstitial oedema and gross lymphatic telangiectasis. Simultaneously, juxtamuscular hyperaemia and oedema appear in the adventitial layer. Round cells, chiefly plasma cells, then infiltrate into the submucosa and, to a less extent, into the serosa, thereafter fibroblasts appear and lay down a markedly argentophil reticulum. As this increases, the round cells disappear, except when they are trapped in aggregations resembling lymph follicles, by rapidly growing reticular tissue. In Schepers's material, round cell infiltration also appeared early in the zone of Auerbach's plexus and swollen nerves were noted in the adventitia and mesentery, leading towards the intestine. In the primary phase no conspicuous reactive changes affected the tunica propria. The secondary phase begins when ulceration and fistula formation complicate the primary lesion at any stage in its evolution. Whereas effective repair may follow extensive but uncomplicated primary infiltration of submucosa and adventitia, once submucosal ulceration and infiltration with polymorphonuclear leucocytes occur, the bowel wall may be progressively and rapidly destroyed. In a critical analysis of possible aetiological factors, the writer suggests that the primary lesion, which may be interpreted as an acute localized vesiculation of the bowel wall, may be due to an irritant metabolite, possibly lipoid in nature, or may more probably result from a neuropathic disturbance involving Auerbach's plexus or the visceral ganglia. Regional ileitis, Schepers suggests, may represent a visceral form of herpes zoster. The evidence for a neuropathic aetiology is discussed. If the neuropathic disturbance involves actual destruction of ganglionic cells, the denervated bowel wall will be exposed to risk of further injury, and tissue destruction, analogous to perforating ulcers occurring in other devitalized tissues, may proceed unchecked.

Treatment

Surgical methods

The short-circuiting method.—Garlock and Crohn review the results of surgical management of regional ileitis, from their experience with 164 cases over a 14-year period. Among 55 primary resections there were 9 postoperative deaths and 9 recurrences, a rate of 19.5 per cent. Some recurrences were medically controllable; two recurred late, 8 and 12 years respectively, after primary operation. Short-circuit procedures, either ileotransverse colostomy or ileosigmoidostomy with transection of the ileum, were adopted in 65 cases, with no death and 9 recurrences, a rate of 13.8 per cent. Two-stage ileocolic resection, consisting of primary short-circuiting ileocolostomy above the lesion with transection of the ileum and later resection of the original diseased area, was done in 25 cases, including 19 cases of combined ileocolitis, with 3 postoperative deaths and 8 recurrences, a rate of 36.3 per cent. In some cases, the second stage was necessitated by failure of the first short-circuiting operation. The specimen when finally removed after a variable interval, in most of these cases showed complete healing. In the interval, abdominal inflammatory masses had dissolved, fistulae had healed and enterovesical communications had closed. The authors therefore consider it to be inappropriate to apply the term, palliative procedure, to the short-circuiting operation, which is to be recommended because of its greater safety and because of the smaller risk of recurrence. Resection was formerly preferred because at that time diagnosis was dependent upon histologic and bacteriologic confirmation of the non-specificity of the lesion, which otherwise was suspected to be tuberculous. With growing experience, ileitis can now be recognized and can be safely short-circuited. No satisfactory medical treatment of ileitis as yet exists. Better results should follow earlier diagnosis and more prompt and experienced surgical intervention.

Garlock, J. H., and Crohn, B. B. (1945) *J. Amer. med. Ass.*, 127, 205.

Schepers, G. W. H. (1945) *Amer. J. digest. Dis.*, 12, 97.

DEAFNESS

See also B E M P, Vol III, p 555, and Cumulative Supplement, Key No 284

Treatment

Otosclerosis

The one-stage operation—At a meeting of the Section of Otology of the Royal Society of Medicine Simson Hall described his experiences of the surgical treatment of otosclerosis. He has finally reverted to a one-stage operation, placing the fenestra over the ampulla and approaching the middle ear by the postauricular route. Heavy premedication with hyoscine and Omnopon followed by light ether has been found to be the most suitable anaesthetic, since it eliminates the slight movements by the patient which are annoying to the operator using the microscope. The operation can be accomplished in two hours. The important part of the first half is the mobilization of the postero-superior portion of the lining of the external auditory meatus and the membrana flaccida in a continuous flap—the “meatal plastic”. Preliminary infiltration of the area with physiological saline and adrenaline solution helps considerably to arrest bleeding. The external meatus is then enlarged and the capsule enclosing the heads of the incus and malleus is incised. After removal of the incus, the head of the malleus is separated. Magnification by microscope or other device is necessary. The labyrinth is trephined and thinning is continued until the endosteum is reached, when the remaining bone and endosteum is removed, revealing the ampulla and canal. The small flap is spread over the fenestra and secured with paraffin packs. The wound is closed completely. A skin graft is inserted about the tenth day and aseptis is practised rigorously throughout the after-treatment. Signs of labyrinthine disturbance persist for days or weeks, most noticeably in older patients. Maximum improvement in hearing is usually attained in about 10 weeks, and averages about 25 decibels. The permanent gain after 2 years is about 15–20 decibels. There is often failure to orientate sounds after the operation. Other speakers expressed doubt of the ultimate results of operation, and the opening of the perilymphatic space was described as uniformly disappointing.

Operation of fenestration—Lempert presents a research study of 1 000 cases in which during the past 7 years fenestration has been performed for clinical otosclerosis, and describes the Lempert fenestra nov-ovalis with mobile stopple operation. Deafness in otosclerosis is usually progressive with final irreparable loss of hearing due to secondary degeneration of the spiral organ. There being no medical treatment fenestration is indicated when the hearing drops below serviceable limits, when there is no active suppuration and when there is evidence of a reserve of cochlear nerve function. The assessment of the latter is discussed, but an accurate test has yet to be discovered. Lempert states that in 300 cases the external semicircular canal was fenestrated and in 700 patients the fenestra nov-ovalis was made in the surgical dome of the vestibule. The results were that serviceable hearing for all social and economic purposes was restored and was maintained in a large percentage of the patients. The improvement of air conduction hearing is maintained subsequently provided that the fenestra is not closed by osteogenesis or that a postinflammatory process in the endolymphatic cases and the study of various techniques used, Lempert proved that it was not necessary to keep the fenestra open, the loss of hearing being caused by the ankylosis of the new bone to the rims of the fenestra, and he also showed that the interposition of a bony stopple in the gap prevents serious postoperative inflammation of the endolymphatic labyrinth. The bony stopple has the disadvantage of acting as a bone graft and Lempert therefore used cartilage and has thus developed the Lempert operation (fenestra nov ovalis with mobile stopple). He has employed this in 50 cases, in which there has been no serious postoperative labyrinthitis and hearing has been improved and—although the fenestra was closed rather than open—has been maintained to the 30 decibel level or higher. To date there has been no evidence of osteogenesis in the fenestra. In the operation described the spine of the helix 0.5 millimetre out of the inner and outer aspects of the fenestra, it should extend position. It is finally covered by the tympanomeatal membrane. Lempert is now adopting the technique in all cases, and states his belief that the results of a large series of cases will prove that his operation will overcome the two principle causes of postoperative failures of other techniques.

Non suppurative conditions

Catarrhal deafness—Wilson considers catarrhal deafness and its treatment. The term includes all forms of middle ear deafness not associated with suppuration or its sequelae, the increase in bone conduction. It is important to recognize this condition in examination of recruits since future experiences in the Forces may produce rapid onset of deafness. Catarrhal deafness is of two kinds: acute catarrhal and true chronic catarrhal. The first form may appear after a simple catarrhal cold, sinusitis or infected tonsils and adenoids. Treatment consists in correction of deflected septum, reduction of enlarged conchae, removal of tonsils, adenoids or nasal polyps. The second group is considered in two categories, (1) hypertrophic and (2) atrophic. In (1) deafness is due to catarrhal hypertrophy of the eustachian mucous membrane caused by recurrent catarrhal attacks or after nasopharyngeal infection. Sudden changes in atmospheric pressure with pre-existing eustachian catarrh will cause a thin mucous exudate

into the middle ear, a condition seen especially in the Royal Air Force. The treatment is to obtain patency of the eustachian tube by catheterization. Mucus in the middle ear may require aspiration through the eustachian tube or by myringotomy. Physiotherapy is of value in reducing congestion of the mucous membrane by short-wave diathermy. (2) The atrophic type shows marked degenerative changes in the tympanic membrane, the anterior part being stretched and the posterior part lax. The sagged part may impinge on the inner wall of the middle ear. By inflation, hearing is improved only temporarily, and the condition deteriorates with increasing deafness.

Hall, I. S., Cawthorne, T., Fowler, E. P., Passe, E. R. G., Howarth, W., and Hutchinson, C. A. (1944) *Proc. R. Soc. Med.*, 37, 737.

Lempert, J. (1945) *Arch. Otolaryng.*, Chicago, 41, 1.

Wilson, C. P. (1944) *Med. Pr.*, 212, 376.

DERMATITIS DUE TO INJURY AND POISONING INCLUDING FEIGNED ERUPTIONS

See also B.E.M.P., Vol. III, p. 609; and Cumulative Supplement, Key No. 290.

Externally applied agencies: direct exposure

Toxic dermatitis

Axillary lesions caused by dress preservers.—Frootko describes a case of contact dermatitis from rubber dress preservers. The patient, aged 20 years, gave a three years' history of recurrent attacks of an irritating rash on both axillae. Although there was no definite seasonal relationship to these attacks, they seemed to be worse in hot weather when the perspiration appeared to be more profuse. The patient was healthy with no evidence of any organic disease. She was of the sympatheticotonic type, with hyperidrosis of the palms, axillae and feet. On examination, the left axilla was covered with an oedematous, vesicular, erythematous plaque which had sharply defined margins. The patient usually wore dress preservers consisting of a sheet of rubber in a cotton casing. The patient was patch tested with a piece of the rubber and in 24 hours a severe vesicular eruption developed on the test area. No further attack has occurred since the use of these dress preservers was discontinued. As rubber itself does not irritate the skin, it seems that the chemicals used to increase the durability of the rubber must be responsible for such a dermatitis in sensitive persons. A patch test should always be made if a contact dermatitis of this nature is suspected and if necessary the specific allergen should be identified.

Due to nail polish.—Keil and Van Dyck point out that the incidence of nail polish dermatitis has increased considerably during the last five or six years. It is suggested that most cases are due to the incorporation of some new ingredient and the authors attribute the cause to a melamine formaldehyde resin which probably contained toluene sulphonamide formaldehyde resin. Of 26 patients investigated by means of patch tests, 25 gave intense positive reactions to a 30 per cent solution of the toluene sulphonamide formaldehyde resin in acetone, whereas 15 control subjects had negative reactions. Hypersensitiveness to the resin was accompanied in some cases by group reactions to related chemical fractions and derivatives such as toluene sulphonamide, formaldehyde and the condensate of these two substances. One patient gave a positive reaction to all three compounds and a weaker reaction to sulphanilamide. It is possible that this patient had been rendered specifically group positive to sulphanilamide, for there was no history of medication with the drug. Another patient was hypersensitive not only to nail polish but also to a straw-hat lacquer containing a gum probably related to the sulphonamide formaldehyde resin. The only other resin to yield positive reactions was melamine formaldehyde resin, applied as a 50 per cent solution in amyl butyrate. It has been found, however, that this resin is plasticized with toluene sulphonamide, combination with the small amount of free formaldehyde forming the sulphonamide polymer. The fact that the reactions were much less intense than were those due to toluene sulphonamide formaldehyde resin probably indicated that the active ingredient was in a smaller concentration.

Frootko, J. (1944) *Clin. Proc. Cape Town*, 3, 340.

Keil, H., and Van Dyck, L. S. (1944) *Arch. Derm. Syph.*, N.Y., 50, 39.

DIABETES INSIPIDUS

See also B.E.M.P., Vol. III, p. 639; and Cumulative Supplement, Key No. 295.

Aetiology and pathology

Investigation of cause

Damage in supra-opticohypophyseal tract.—Jones emphasizes that diabetes insipidus is a symptom complex produced by damage along the supra-opticohypophyseal tract which interferes with secretion of the antidiuretic principle by the posterior lobe of the hypophysis; the disease requires investigation for the purpose of establishing, if possible, the exact aetiology. Forty-two patients, in each of whom there was a minimum daily fluid intake and output of 6,000 and 4,000 cubic centimetres respectively, the urinary specific gravity never exceeding 1.008, were investigated. Fairly marked clinical or pathological evidence of involvement of the supra-opticohypophyseal tract was found in 33 patients; 11 had tumours involving the hypophysis, 2 being verified at necropsy. Tumours involving the hypothalamus in 2 cases, xanthomatosis in 4, chronic encephalitis in 7, syphilis in 3, posttraumatic head injury in 3, and one case each of hypophyseal infarction, cerebrovascular accident and subarachnoid

haemorrhage, were other findings. Signs suggestive of hypothalamic organic change of unknown aetiology occurred in another patient. No aetiological diagnosis was established in 8 cases, in 2 of which the possibility of psychogenic origin was eliminated by the patients' response to urine concentration tests. Patients with diabetes insipidus, receiving a limited fluid intake, continue to secrete urine of low specific gravity with resultant loss of weight. Roentgen irradiation in cases of neoplastic aetiology or of xanthomatosis, and antisiphilic therapy if indicated, were effective procedures in several cases in this series. Since polyuria preceded other evidence of malignancy by 8 months and 6 years in 2 of his cases, Jones advises roentgen irradiation of the hypothalamico-hypophyseal region in cases of diabetes insipidus of undetermined aetiology. Replacement of the antidiuretic principle in the form of intramuscular Pitressin tannate in oil or posterior pituitary solution hypodermically gave good symptomatic relief. Pitressin given intranasally was much more effective in solution than in jelly form. An average daily dose of 2.5 cubic centimetres of Pitressin solution was given.

Jones, G. M. (1944) *Arch. intern. Med.*, 74, 81

DIABETES MELLITUS

See also B. E. M. P., Vol. III, p. 644, and Cumulative Supplement, Key No. 296

Diabetes mellitus

Pathogenesis

Experiments with secretions of the anterior lobe of the hypophysis—Young emphasizes the possible significance in diabetes mellitus of the relation between growth-stimulating and diabetogenic actions of secretions of the anterior lobe of the hypophysis. The author's experiments demonstrated that the administration to puppies of an anterior pituitary extract which is diabetogenic to adult dogs, in 75 per cent of puppies treated caused acceleration of growth but not diabetes until, under continuous anterior pituitary administration, diabetes developed when they attained adulthood and ceased to grow. Administration of anterior pituitary extract and insulin then caused increase in weight but very large doses of insulin were required to control the diabetogenic action of the anterior pituitary extract. One dog, for example, needed more than 2,000 units of protamine zinc insulin per day in order to suppress the diabetogenic action of daily subcutaneous injection of 5 millilitres of anterior pituitary extract which, during the first 20 weeks of the experiment, had induced abnormal growth but not diabetes. The investigation suggests that during the period of growth stimulated by administration of anterior pituitary extract, the puppies were secreting more insulin than they would have done under conditions of normal growth. At any rate, daily injection of diabetogenic anterior pituitary extract into diabetic or prediabetic adult dogs produced a pronounced insulin-insensitive condition. In one subject, early in the course of the experiment there developed an enlarged thyroid gland, but diabetes did not develop even after anterior pituitary extract had been administered for nearly 11 months, the animal continued to grow throughout the duration of the experiment.

Aetiology

Review of causative factors—In reviewing the aetiology of diabetes mellitus, Ogilvie first considers the part played by the pancreas, in which various pathological changes have been detected. The pancreatic islets in 26 per cent of diabetic subjects are histologically normal, which suggests that the cause of islet changes lies primarily in an extrapancreatic disturbance. Investigation of the influence of the hypophysis in carbohydrate metabolism was also undertaken. Administration of anterior pituitary extract to normal subjects caused development of diabetes, their pancreatic islets then showing degenerative changes comparable to those found in human diabetes. Besides its diabetogenic factor, anterior pituitary extract evidently contains glycotrophic, ketogenic and pancreatrophic principles. The observations suggest that the diabetic syndrome is due to a complex of these factors, secreted in excess. Diabetes may be initiated by transitory hyperfunction of the anterior lobe of the hypophysis and maintained through pancreatic islet degeneration and insulin deficiency. Observation that diabetes is commonly preceded by abnormal growth vertically in children and laterally in adults suggested that a balance normally exists between pancreatic and hypophyseal influences. Recent investigations indicate that such growth represents a protective mechanism whereby nitrogen and carbon retained in consequence of excessive anterior lobe activity are stored as extra tissues under the influence of the hyperfunctioning pancreatic islets so long as pituitary hyperfunction is neutralized by corresponding overactivity of pancreatic islets, which ultimately become exhausted and even permanently degenerated. Thus failure of the elevated hypophyseal-pancreatic balance expresses itself in diabetes mellitus. The influence of the thyroid gland and the ovary on carbohydrate metabolism is mentioned by the author, and emphasis is laid on the suprarenal cortex as exercising a control on carbohydrate metabolism almost as great as that exerted by the anterior lobe of the hypophysis. Finally, the finding that alloxan, which is related to certain agents and functions in the body, can experimentally produce diabetes may soon shed new light on the aetiology of diabetes mellitus.

Further experiments with alloxan—Goldner and Gomori report on experiments in which dogs and rabbits were given alloxan for the purpose of producing diabetes mellitus. Chemically related compounds were also tested but none had an effect similar to that of alloxan. Injections of protamine zinc insulin failed to prevent degeneration of the islands of Langer-

hans in alloxan-treated animals but proved to be adequate to control the hyperglycaemia. The experiments indicated that the early hyperglycaemia is not a causal factor in the development of diabetes mellitus, since prevention of the rise in blood sugar does not protect against degeneration of the cells in the islands of Langerhans. There is no evidence that insulin is inactivated by alloxan *in vitro*. It is probable, therefore, that the initial hyperglycaemia is not due to lack of insulin but to mobilization of extra glucose. It is believed that the formation of glucose results from stimulation of hepatic glycogenolysis by adrenaline. This hypothesis was tested by injecting alloxan into rabbits after the removal of the medullary portions of the animals' suprarenal glands. In no instance did severe hyperglycaemia develop. All the animals died after typical hypoglycaemia convulsions. A hypoglycaemic phase occurs after the hyperglycaemia produced by injections of alloxan. Examination of the pancreas showed that degeneration of the β cells precedes this phase and that the insulin content of the gland is considerably reduced. The hypoglycaemia is not due to the insulin-like effect of alloxan, because the level of the blood sugar does not fall after the compound is given to animals subjected to pancreatectomy.

Treatment

Effect of prolonged diabetic treatment.—A study was made by Richardson and Bowie of 100 patients with diabetes for 10 years or more, who had been under close observation at a University of Pennsylvania medical clinic for many years. The investigation was undertaken because the patients had been maintained on a diet in which the carbohydrate had been increased and the fat decreased, in comparison with diets previously in general use. Examined first in the metabolic section of the clinic the patients were then referred to the cardiac, the peripheral vascular and the ophthalmological sections, under the care of Edeiken, Naide and Leopold, respectively. The fat in the diet varied between 70 and 110 grammes, with an average of 90 grammes, the carbohydrate between 125 and 200 grammes; the protein had been gradually increased up to an average of 70 grammes daily. The patients were divided into 4 groups, those who did not take any insulin, those using up to 25 units daily, those having from 25 to 50 units, and those requiring 50 or more units of insulin per day. It was found that in at least 45 per cent of the patients there was no increase in the severity of the diabetes. Although neither the duration nor the severity of the disease appeared to influence the incidence of hypertension, infection or ocular sclerosis, the incidence of deep retinal haemorrhages and exudates, and superficial haemorrhages in the eyes appeared to be increased by diabetes. The incidence of cardiac enlargement in the patients with hypertension was about half of that found in non-diabetic hypertensives. In the patients under 50 years of age the incidence of cardiovascular disease was lower than is usually found in diabetics, a finding suggestive of the value of the high carbohydrate-low fat diet in reducing the premature cardiovascular abnormalities. Although the patients in the group studied had had diabetes for periods varying from 10 to 25 years, none had required amputation of a toe or leg, a result attributable to prophylactic care of the feet and to the use of sulphonamides, as well as to adequate control of the diabetes. Arteriosclerotic occlusive disease of the lower extremities was found in 45 per cent of the female patients and in 22 per cent of the male. The much higher incidence in diabetic than in non-diabetic women is paralleled by the commoner occurrence of coronary disease in diabetic women.

Dietary control.—Burn, Lewis and Kelsey stress the advantages of alloxan injection over other methods of inducing experimental diabetes. By varying adjustments of the diets fed to rats made diabetic by alloxan, the authors demonstrated first of all the effect upon urine dextrose excretion of reduced calorie intake *per se*, regardless of fat, reduction of which in stages from 60 per cent of the diet down to 30 per cent did not increase glycosuria, because the unpalatability of the experimental diet caused lack of appetite and consequent calorie reduction. On change of diet and fourfold increase of calorie intake dextrose excretion more than doubled. On reduction of calorie intake to one-ninth, approximately, dextrose excretion again fell to a low figure. Margarine was next incorporated in a normal palatable diet to 20 per cent, then gradually up to 70 per cent. As the fat percentage rose the mean daily dextrose excretion steadily fell. With 60 per cent of margarine it was as low as 0.3 gramme per diem and at 70 per cent excretion ceased. The diet was so manipulated that the total calorie intake fell only slightly. In the rat ketonuria develops less readily than it does in man. Acetone bodies were sought in the urine after each change in diet. Ketonuria occurred on one day only during the 8 weeks' experiment when the fat content of the diet had been increased to 50 per cent. It was absent when the fat was further increased to 60 and 70 per cent. After successive periods of a diet rich in fat glycosuria steadily diminished. Further work is proceeding to determine whether or not high fat diet restores functional islet tissue in rats.

Globin insulin.—Eaton describes treatment with globin insulin of 10 in-patients and 31 out-patients with diabetes mellitus, most of whom were selected because of treatment difficulties which had been encountered with other types of insulin. Twelve patients had had hypoglycaemic reactions and 3 had had troublesome local reactions when they were on protamine zinc insulin; 8 had responded badly to protamine zinc insulin or protamine zinc insulin plus soluble insulin. As the diets previously adjusted to suit treatment with protamine zinc insulin were unchanged after admission to hospital the results, in the in-patient group, demonstrate merely the relative, not the best, effects of insulins other than protamine zinc

insulin on patients all taking the same diet. The in-patients' blood sugars were estimated 2 hourly between 8 a m and midnight and 4-hourly between midnight and 8 a m. On mixtures of protamine zinc insulin and soluble insulin the uniformity of the blood sugar during the 24 hours was greater than it was on globin insulin and hyperglycaemia was well controlled without nocturnal hypoglycaemia, the mixture, however, entails complicated dosage and consequent greater liability to error. Maximum blood sugars were almost identical on protamine zinc insulin or globin insulin but there was a lower minimum on the former. Amongst the out patients, who were all treated with globin insulin, hypoglycaemia occurred between 11 a m and noon and between 4 p m and 6 p m, but during the night in only one patient who had globin insulin in the evening for convenient injection. The alteration by the advancing of the daily distribution of the carbohydrates reduced hypoglycaemia, the incidence of which, the author suggests, would probably be reduced also by further dosage experience. Local reactions to globin insulin are less than to other forms and no case of atrophy of subcutaneous fat has been reported. One patient was allergic to globin insulin as well as to soluble insulin and protamine zinc insulin. Globin insulin has a quicker and less sustained action than has protamine zinc insulin.

Diabetes in children

Treatment

Nutrition and feeding standards—Barach, before discussing the problem of planning for the nutritional restoration of diabetic children and for the maintenance of a normal nutritional level throughout the remaining period of their growth, attempts to find acceptable values for height and weight standards of children at various ages. He presents growth charts, constructed on the basis of averages obtained from measurements of over 400,000 children, which portray the normal trends of growth. After reviewing the generally accepted standards for daily calorie and protein requirements per kilo of body weight for growing children at different ages, Barach suggests for diabetic children a diet of adequate calorie, protein, fat and carbohydrate portions based on the normal body weights in successive years. Each food value approximates to the normal level as nearly as possible provided that the calorie value of the fat portion never exceeds the calorie value of the combined carbohydrate and protein. The growth curves of 135 diabetic children, who had been under observation for 2-12 years, were superimposed on the normal growth charts, and showed that 25 were within normal limits, 57 were undersized and 53 oversized. The calorie values of the diets on which these children had been subsisting were then compared with the maintenance diets calculated by Barach as being required for diabetic children. Nine children had attained normal growth on diets of lower calorie value than Barach's minimum diet, and 16, despite excessive diets did not exceed normal growth. Of the undersized children 30 had less than the minimal and 27 had no more than the full minimal requirements. Of the oversized children 31 received the maximum and 22 more than the maximum diet recommended. Thus a positive relationship exists between dietary calorie values and children's growth. The generously fed and the conservatively fed required, respectively, an average of 55 and 32 units of insulin daily.

Diabetic coma

Treatment

Diabetic coma and giving of glucose—Root, reporting on a series of 601 cases, discusses the treatment of diabetic coma. In 478 cases up to August 1940 the case mortality rate was 12 per cent, in a subsequent series of 123 consecutive cases there were only 2 deaths. Root believes that this low mortality is the result of the earlier administration of larger doses of insulin. The average dosage of insulin during the first 3 hours has risen steadily from 83 units to 216. The crux of the treatment of diabetic coma is to convert the large amounts of glucose present in the blood and body tissues into energy and glycogen. The author, with Carpenter, has shown that the giving of glucose does not increase the oxidation of carbohydrate during coma. It is believed that the usual practice of giving 50 grammes of glucose or more in coma is harmful since only 5-10 grammes can or need be oxidized hourly to check ketone formation, one reason, amongst others given, being that glucose neutralizes the insulin and the rise of the blood sugar makes the calculation of the insulin dosage difficult. Treatment of a patient should be undertaken in a hospital in which adequate facilities should be available. When it is learned at the hospital that a patient is to be brought in, if the diagnosis is reasonably certain, a dose of 20-60 units is given by the patient's doctor or by a member of the family. Estimation of the required dosage on admission is difficult as insulin resistance increases with acidosis and the law of diminishing returns applies to insulin. Urine and blood sugar tests should be carried out every 2 hours, and after adequate initial dosage has been given further dosage can be planned on a schedule based on the reaction to Benedict's test. The dehydration and shock syndrome must be treated with isotonic sodium chloride solution given intravenously or subcutaneously. Gastric lavage should be done and enemata given. Feeding by the mouth if possible is started 4-6 hours after admission, but if this is not possible and an adequate dose of insulin has been administered, glucose, previously contra indicated, can be given intravenously for food requirements 6-12 hours later.

Factors complicating the treatment of diabetes

Infections

Penicillin in pyogenic infections—Peck discusses the use of penicillin in the management of pyogenic infections associated with diabetes mellitus. Local infiltration of the infected area

was found to be very effective. The method was of particular efficacy in the treatment of carbuncles and in several instances the lesion resolved without the formation of a slough. In some cases intravenous or intramuscular administration was inadequate, but supplementary injections into the necrotic mass resulted in rapid clearance of the lesion. Mere irrigations were not enough, since in order to exert a full effect penicillin must be in contact with the organisms for several hours. In the treatment of osteomyelitis associated with a sinus satisfactory results were obtained by using a syringe to force the solution into the tissues every 3 hours. Drainage was prevented by the application of adhesive tape. Twelve patients were treated successfully and these included cases of the septic type of gangrene, osteomyelitis of the bones of the feet and huge carbuncles. In no instance was there any deterioration in carbohydrate tolerance nor were larger doses of insulin required as a result of treatment with penicillin. Three cases proved to be fatal but the deaths could not be attributed to the failure of the drug. In one case insufficient penicillin was available and the other two patients were in a moribund state on admission. At first, the solution employed ranged in strength from 100 to 250 units per cubic centimetre. Subsequently, however, the potency was increased to 1,000 units per cubic centimetre. The total dosage varied from 20,000 to 800,000 units. It is emphasized that the use of penicillin does not relieve the clinician of the necessity of adopting all the precautions necessary to proper treatment of infections. Drainage must be established surgically and it is essential to determine the causal organism.

Barach, J. H. (1945) *Amer. J. Dis. Child.*, **69**, 92.

Burn, J. H., Lewis, T. H. C., and Kelsey, F. D. (1944) *Brit. med. J.*, **2**, 752.

Eaton, J. C. (1944) *Lancet*, **2**, 269.

Goldner, M. G., and Gomori, G. (1944) *Endocrinology*, **35**, 241.

Ogilvie, R. F. (1944) *Edin. med. J.*, **51**, 460.

Peck, F. B. (1944) *Amer. J. med. Sci.*, **208**, 581.

Richardson, R., Bowie, M. A., Edeiken, J., Leopold, I. H., and Naide, M.

(1945) *Amer. J. med. Sci.*, **209**, 1, 8, 16, 23.

Root, H. F. (1945) *J. Amer. med. Ass.*, **127**, 557.

Young, F. G. (1944) *Brit. med. J.*, **2**, 715.

DIARRHOEA

See also B.E.M.P., Vol. IV, p. 1; and Cumulative Supplement, Key No. 305.

Clinical picture

Epidemic diarrhoea of unknown cause

Diagnosis and treatment.—Reimann, Hodges and Price discuss a syndrome of epidemic diarrhoea, nausea and vomiting, of unknown cause, which has been described as occurring in the United States of America, Germany, Canada, Great Britain, Denmark, Australia and elsewhere. They define it as almost certainly "a widespread, communicable, endemic, sporadic and at times epidemic disease or group of diseases, apart from the known forms of dysentery and acute food poisoning, which because of its mildness usually passes unnoted in the press and of other problems". Investigations have failed to reveal a cause but the authors suspect, as do numerous other observers, an unknown enterotropic filtrable virus or viruses and regard the condition as a non-seasonal, contagious and infectious disease, affecting predominantly the gastro-intestinal tract. The infection is probably airborne. It occurs at all ages but notably in children of school age and young adults. Symptoms in order of frequency are usually anorexia, nausea, vomiting, diarrhoea, dizziness, aching and abdominal discomfort or cramps; there are sometimes chilliness and fever and, rarely, symptoms or signs of upper respiratory tract infection, bradycardia and constipation. Onset may be very abrupt, and giddiness, likened by several observers to that of seasickness, may be severe. The syndrome must be differentiated (1) when in epidemic form, from bacillary dysentery or food poisoning, and (2) when sudden nausea, vomiting, pyrexia, right lower quadrant abdominal pain and leucocytosis are present, from acute appendicitis. Treatment by rest in bed, local application of heat for relief of abdominal pain, and restriction of diet usually suffice, but administration of camphorated tincture of opium relieves protracted diarrhoea and pain.

Reimann, H. A., Hodges, J. H., and Price, Alison H. (1945) *J. Amer. med.*

Ass., **127**, 1.

DIARRHOEA IN INFANCY AND CHILDHOOD

See also B.E.M.P., Vol. IV, p. 21.

Pathology and bacteriology

Bacteriology

Pathogenic significance of the paracolon bacilli.—Neter and Clark discuss the part played by paracolon bacilli in diarrhoeal diseases. They isolated the bacilli from 49 infants and children, 39 of whom had diarrhoeal symptoms. In 25 cases no other pathogenic, or potentially pathogenic, organisms existed in the faeces. Paracolon bacilli are known to occur in persons without evidence of diarrhoeal disease and in cases in which they do exist in the faeces in association with symptoms their presence is not evidence of pathogenicity. They may be merely saprophytes or may play only a secondary part as incitants of disease, since they are found frequently in association with enteric pathogens. There is the added difficulty that not all patients develop specific antibodies against infecting micro-organisms and therefore the absence of agglutinins against paracolon bacilli does not necessarily disprove their

pathogenicity Previous studies in institutional diarrhoea have suggested that the organisms may be pathogenic, particularly in cases in which they have been isolated in outbreaks from both patients and persons who handled food. The occurrence of paracolon bacilli in infants and small children with diarrhoeal disease raises the question whether or not individuals of that age group are less resistant towards the organism than are older children and adults. Of the 39 cases with diarrhoeal symptoms in this series, 33 were infants one year of age or less. The possible pathogenic significance of paracolon bacilli may be easier to interpret when it is known to what extent they occur in the intestines of infants free of diarrhoeal disease.

Clinical picture

Infective influences

Dangers of dehydration—Alexander and Eiser review 140 cases of diarrhoea and vomiting which occurred in infants under 15 months of age. Males predominated in the ratio 3:2. The severity of the disease was greatest in the first 9 months of life, especially in premature infants. The illness was seldom as severe in breast fed infants as it was in artificially fed babies. Moreover, recovery was quicker and usually uncomplicated. Parenteral infection was an inciting agent in 124 cases and sometimes a comparatively trivial primary infection was responsible for setting up a disproportionately violent reaction of diarrhoea and vomiting. There were 69 cases of dehydration, with a fatality rate of 11.6 per cent. Confirmation of fluid loss was afforded by a raised blood urea and a low alkali reserve, but not by haematocrit readings. Most of the 27 relapses were more severe than were the primary attacks, notably in infants nursed in wards with the barrier system of isolation. Eight deaths in the series included 2 cases of death due to circulatory failure caused by excessive parenteral fluids. The unfavourable sign of orange coloured stools was noted in 6 infants and death occurred in one of these cases. Plasma tests showed protein deficiency and it is possible that the fatty liver found at necropsy may be associated with lack of proteins and amino-acids. A warning is given against too enthusiastic serum therapy, for continuous infusion of proteins may precipitate circulatory embarrassment by raising the osmotic pressure of the blood and causing tissue fluids to be drawn into the blood stream. The good results obtained in this series are attributed to the prevention and treatment of parenteral infection, dehydration and anaemia. The best prophylaxis consists in breast feeding for at least the first 6 months of life combined with protection from exposure to infection.

Treatment

Administration of fluids

Transfusions into the tibial marrow cavity—Gunz and Dean following the technique described by Gimson, record their experience of 35 transfusions into the marrow cavity of the tibia in small children who have been dehydrated as a result of gastro enteritis. Full surgical precautions were taken against sepsis and the skin was thoroughly sterilized by spirit. There was some difficulty in choice of needle because of the uncertain depth of the subcutaneous tissue. The site chosen for the injection was at least 1 inch below the level of the tibial tuberosity. Saline, glucose saline, Hartmann's solution and half strength serum have given good results. As a rule the rate of the drip needed to be slowed in order to prevent onset of oedema. The rate of flow should automatically slow as the body fluids become replenished. If the needle becomes blocked, it should be cleared by sucking through it by means of a 2 millilitre syringe a small amount of the fluid from the bone marrow cavity. There is always the danger of causing an osteomyelitis if there is the least relaxation of strict surgical asepsis. In 2 out of 3 cases in which blood was transfused into the tibia osteomyelitis developed. The use of the intramedullary drip requires skill and practice in order to obtain the best results. It can be quickly put in operation but needs careful supervision in acceleration of the rate and in control of the flow. The onset of oedema in many cases necessitates the abandonment of the drip. The conclusion is reached by the authors that intramedullary tibial transfusion is a valuable alternative to intravenous therapy but that it is not suitable for the transfusion of blood.

Drugs

Successful results with sulphaguanidine—Campbell reports on useful experience gained during an epidemic in Melbourne of diarrhoea affecting 50 newborn babies of whom 32 were breast fed. The characteristic stool was a yellow fluid containing no faecal particles or mucus, quite unlike an ordinary diarrhoeal stool. The first outbreak spread with explosive rapidity among 11 premature babies. There was delay in instituting treatment which consisted of initial starvation, free fluids given orally and the intravenous injection of glucose-saline. Feeding commenced with much-diluted sweetened condensed milk. Nine babies died. Necropsy performed on 2 infants showed evidence of overloading of the vascular system. In the second attack, affecting 8 premature and 20 full time babies, similar treatment was instituted promptly, but parenteral fluid was administered at a more carefully controlled rate. The continuous subcutaneous drip method proved to be satisfactory. Only 2 premature infants died. The third outbreak, affecting 10 premature babies and 1 full time infant, gave an opportunity to test the efficacy of sulphaguanidine therapy. The average duration of illness in babies treated with sulphaguanidine was 3 days as against 8½ days in the previous series and the whole severity of the disease was strikingly reduced. At necropsy, intestinal inflammation of varying severity, depending on the duration of the disease, was noted. No recognized

pathogenic bacteria were isolated from the stools. Scrupulous care in the technique of feeding, preparation of feeds and disposal of napkins failed to check the spread of the disease, for which strict isolation was essential. Several babies had a frothy nasal discharge. In retrospect, it may have been significant that, coincidentally with this epidemic, there was an outbreak of "gastric influenza" amongst the adult population. Campbell, after reviewing the literature relating to aetiology, suggests that parenteral infection, to which premature babies are particularly susceptible, causes the derangement of intestinal functions and that thereafter the normal bacterial bowel content invades the jejunum, develops pathogenic properties and produces enteritis.

Alexander, M. B., and Eiser, Y. (1944) *Brit. med. J.*, 2, 425.

Campbell, Kate I. (1945) *Med. J. Aust.*, 1, 79.

Gunz, F. W., and Dean, R. F. A. (1945) *Brit. med. J.*, 1, 220.

Neter, E. R., and Clark, Phyllis (1944) *Amer. J. digest. Dis.*, 11, 356.

DIETETIC DEFICIENCY DISEASES

See also B.E.M.P., Vol. IV, p. 51.

Prevalence of deficiencies

Deficiencies in America

Shortage of vitamins and malnutrition.—Murneek states that malnutrition is prevalent in the Northern United States of America owing to the shortage of vitamins, a shortage largely produced by the refining processes in the manufacture of modern foods. In many cases the process of purification has been carried so far that in thousands of people deficiency diseases would develop were it not that other foods are eaten—fruits, vegetables and dairy products. Prolonged fermentation was formerly an essential step in the preparation of certain foods, and it is known that yeast has the capacity to take part in the formation of dietary factors. Some choice varieties of food plants have disappeared from the markets because the products were not of a desirable appearance and were too tender for distant transportation or for prolonged storage. On the other hand, attempts are now being made to increase the vitamin content of plants grown for food. Stringent regulations have been promulgated in order to ensure the maturity of fruits, and there has been a revival of interest in wild plants, especially those rich in vitamins. Ample evidence exists that the vitamin content of fresh produce is decreased by delayed use. Speedier transportation and better refrigeration may overcome the difficulty. Cooks should pay attention to the advice of nutrition specialists who emphasize that prolonged heating has a deleterious effect on the vitamins. Very little water should be used in cooking vegetables and fruits. Many vitamins are now manufactured *in vitro* and are available under chemical names. According to Kretschmer, the people of the United States of America are spending a quarter of a billion dollars annually on vitamin pills and tablets. It would be a safer plan to rely on man's natural instinct for good food, in spite of the modifications that have developed as a result of modern social and economic forces.

Deficiency of vitamin A

Clinical picture

Effect on eyes and skin.—Sheard, Wagener and Brunsting discuss disturbances of visual adaptation and their clinical significance from the ophthalmological and dermatological aspects. Study of the biophysical and physiological measurements and responses of rods and cones in visual adaptation suggests that the three fundamental factors which may exert an influence on dark adaptation are: (1) pigment or pigments and the conditions which may affect the photochemical reaction and changes; (2) the metabolism and nutritional state of the body and of the retina as a localized site of pigment and photochemical reaction; (3) the neural and cerebral responses exhibited in anoxia and in problems of aviation medicine. The authors quote Krause's statement that "the metabolism of the retina is similar to that of the brain, and not of other tissues. This is to be expected since the retina is anatomically a part of the brain. Weinstein reported that in the retina and brain the oxygen consumption and carbon dioxide production aerobically and anaerobically are similar." Vitamin A is a constituent part of the photosensitive pigment or pigments of the rods and probably also of the cones. Abnormal dark adaptation can be improved by administration of vitamin A; night blindness can be produced, in some instances, by diet deficient in vitamin A. In the absence of organic eye disease critically standardized and controlled dark-adaptation measurements aid diagnosis of avitaminosis A due to dietetic deficiency, of functional deficiency or transfer of vitamin to the retina and of lack of hepatic vitamin reserves or unavailable reserves. Previous researches have shown that, although dietary deficiency of vitamin A is not readily induced in healthy and nutritionally stable people, if avitaminosis A—as measured by dark-adaptation thresholds—is induced it is likely to occur in a few weeks on deficient diet and that even with large oral dosage of vitamin A recovery may be delayed for several months. The dark-adaptation levels of some patients afflicted with rare familial dyskeratotic skin diseases have been found to be elevated from threefold to twentyfold, which shows that there is a disturbance of the metabolism of vitamin A.

Deficiency of the vitamin B complex

Diseases directly due to vitamin B deficiency

Hyporiboflavinosis.—In the Lumleian Lectures delivered before the Royal College of Physicians in London, Stannus discusses problems in riboflavine and allied deficiencies. He bases a

tentative explanation of the pathogenesis of the signs and symptoms of riboflavin deficiency and of their localization, on an anatomicophysiological consideration of the capillary vascular system. Over 30 years ago Stannus described an outbreak of pellagra in Africa and noted the occurrence of a group of symptoms—soreness of the tongue and lips with a characteristic lesion at the corners of the mouth, the nostril, the palpebral fissures, the free border of the prepuce, the vulva and the anus and dermatosis of the scrotum—which often developed before the onset of pellagra. Other observers linked up neurological symptoms, peripheral neuritis, deafness and blindness with dietetic deficiency. Stannus considered hyporiboflavinosis to be a convenient term for the condition in question, although the possibility that some other factor as well as riboflavin is at work cannot be excluded. Riboflavin is held to be present in the cells of every tissue in the body and, combined in the form of a flavoprotein, acts by alternately accepting and releasing two atoms of hydrogen, and so participates in a number of reactions with carbohydrate metabolism. The great importance of the capillary system in the economy of the body is often not recognized. It may be assumed that the capillary endothelial cells require all the elements needed by other cells for their normal metabolism and it is suggested that this tissue is the first to suffer from riboflavin deficiency which results in dilatation of the veins and impaired flow, which in turn causes interference with the normal cellular metabolism and a derangement of tissue function. The interference is probably of the nature of an anoxia in its wide sense and the derangement is greatest in tissues most richly supplied with capillaries. Stannus gives evidence to suggest the causation of the neurological symptoms of the syndrome under discussion, chief among them being a sense of muscular weakness, incoordination, ataxia and paraesthesiae, not associated with any real loss of power or sensation or with any muscular wasting, as well as the loss of visual and auditory keenness.

Masking of signs—Merrill emphasizes the masking of signs and symptoms of vitamin B deficiency by the apparently more important precipitating conditions. He stresses that such deficiency should be sought under conditions of increased metabolism, defective diet and disturbed gastro-intestinal function and should be corrected before the stage of non reversibility is reached. He cites 8 cases encountered in 7 years' private practice in which avitaminosis B was diagnosed as follows: (1) Pneumonia (2) Alcoholism and morphine addiction, (3) Profound malnutrition from chronic diarrhoea, vomiting, and extensive liver metastases secondary to colonic carcinoma (4) Glossitis of 11 years' standing which responded to administration of liver extract although not of yeast, nicotinic acid or riboflavin (5) Neuritis in an obese man on an excessively high calorie diet (6) Scarlet fever (7) Pre-operative starvation (8) Postoperative starvation. In this last case the author suggests the possibility that vitamin B deficiency may have contributed to postoperative gastric dilatation, intestinal distension and ileus and impaired bladder function. The author considers that vitamin B deficiency was, in some cases, accentuated by intravenous glucose administration. Other precipitating or contributory factors were fever, bizarre diets, chronic diarrhoea, poor teeth or faulty dentures, pre-operative apprehension, excessive hours of manual labour, diets over-rich in starch, and sore throat or sore mouth, more than one of these factors were usually operative. In dilating on the scarlet fever case he suggests that scarlet fever heart and the milder forms of beri beri heart, as described by Weiss and Wilkins, may be identical conditions, and he attributes the excellent prognosis in scarlet fever heart to the fact that when the acute sore throat subsides the patient begins to eat.

Syndromes due to dietetic deficiencies as yet not finally identified

Kwashiorkor

Malignant malnutrition—A common malnutritional disease among negroes of Central Africa is termed by Trowell "the syndrome of malignant malnutrition". Maximal incidence occurs in the second and third years of childhood. Cases appear among adults, for example among immigrant labourers who are experiencing difficulty in securing food. Skin pallor and fading of the hair, which softens and straightens, occurs in children. Darkly pigmented dyskeratotic patches develop on skin sites of irritation. Children fail to grow, adults become cachectic. Advanced cases show oedema, not attributable to heart failure or nephritis, but apparently due to hypoproteinaemia. In 20 of the author's patients—adults and infants—and in advanced cases passed loose faeces having undigested protein, starches and fat. Radiological visualization showed irregularly segmented intestines, manifestations of grave cases, signs of peripheral neuritis and marked mental depression occurred. In advanced adult cases contracted and potentially were rapidly fatal, especially pneumonia. Infections were 3,000 calories, containing 100 milligrams of protein and supplementary vitamins, usually cured moderate cases, provided intercurrent infections, especially malaria, helminthiasis and amoebiasis, were treated successfully. Patients in advanced cases required 5-10 milligrams of aneurine daily in order to relieve severe anorexia and allow intake of the necessary diet. Prothylolised liver or predigested meat were necessary. Mersalyl benefited oedematous patients. Diarrhoea of inflammatory origin required chemotherapy, purgatives being contra-indicated. Diarrhoea due to malnutrition might be terminal or might respond to crude liver extracts given parenterally. Full diet had to be maintained throughout, but did not cure very advanced cases in which a vicious circle of anorexia and inability to digest and assimilate food had

been set up, owing to grave gastro-intestinal defects. At present the relationship of this syndrome to other malnutritional diseases, such as pellagra, beri-beri and nutritional hypoproteinaemia, cannot be stated.

Merrill, D. (1944) *New Engl. J. Med.*, 231, 174.

Murneek, A. E. (1944) *Science*, 100, 557.

Sheard, C., Wagener, H. P., and Brunsting, L. A. (1944) *Proc. Mayo Clin.*, 19, 525.

Stannus, H. S. (1944) *Brit. med. J.*, 2, 103, 140.

Trowell, H. C. (1944) *Clin. Proc.*, Cape Town, 3, 381.

DIPHThERIA

See also B.E.M.P., Vol. IV, p. 72; and Cumulative Supplement, Key No. 324.

Clinical picture

Cutaneous and wound diphtheria

Report of a fatal case.—Harley and Zia-Ullah describe a fatal case of skin diphtheria. Chronic ulceration of the skin caused by diphtheria is rare. An untreated ulcer has a dry blackish membranous and gangrenous slough, with a surrounding area of redness and oedema. The slough is leathery and difficult to remove, the underlying ulcer is indolent, with red and heaped-up edges and a hollowed-out and fairly deep base. The patient in the case described, a man aged 33 years, fell off his bicycle and sustained trivial superficial wounds of the right leg, which were dressed but did not heal. After a week the patient was admitted to hospital with a high temperature and with an area of cellulitis round the wounds. A week later, two painful and tender ulcers covered the wound sites, with black eschars and undermined and unhealthy margins. Treatment with M and B 693 (sulphapyridine) and various applications to the ulcers did not cause improvement, the patient's condition rapidly deteriorated and he showed signs of heart failure. Skin diphtheria was diagnosed and large doses of anti-diphtheritic serum were given, but without avail. Smears from the ulcers showed Klebs-Loeffler bacillus in direct examination and in pure culture; no secondary infection was present. Paralysis occurs in 15 per cent of cases of cutaneous diphtheria, but circulatory failure is rare.

Harley, H. R. S., and Zia-Ullah, M. (1944) *Guy's Hosp. Rep.*, 93, 59.

DISLOCATIONS, FRACTURES, FRACTURE-DISLOCATIONS, AND ASSOCIATED INJURIES

See also B.E.M.P., Vol. IV, p. 113; and Cumulative Supplement, Key Nos. 326-353.

Treatment

Union

Use of metal in orthopaedic surgery.—McKee reviews the use of metals in orthopaedic surgery. When first introduced under aseptic technique this form of fixation was received with enthusiasm but was quickly discarded when inflammation and abscess formation ensued: it was soon recognized that these were not necessarily bacterial in origin but were due to electrolytic and chemical reactions between the metals and the tissues. It was found that the purest metal created the least reaction. A metallic alloy, vitallium, is extremely resistant but has mechanical disadvantages. Recently a pure metal, tantalum, has been introduced, but some discoloration of the tissues around the metal has been shown to take place. The ideal metal should not give rise to any reaction in the tissues. Non-corrosive metals are now being widely used in special and difficult fracture repair. They serve the purpose of fixation of the fragments, permitting the maintenance of function. The utility of the Smith-Petersen pin for fractures of the neck of the femur was immediately recognized, and started the revival of internal fixation for other types of fracture. Metallic fixation is used for fractures of the shafts of long bones and in oldstanding cases of non-union, bone grafts can be held in position by means of screws. The Smith-Petersen pin is successful in 70 per cent of cases. Internal fixation of pertrochanteric and subtrochanteric fractures has many advantages and there is no liability to aseptic necrosis. Metal is used as a means of fixing joints and of creating new joints. Metallic wire is also suitable for suturing tissues, nerves and tendons.

Use of external pin fixation.—Siris reviews and analyses the results obtained in 80 cases of external pin fixation of fractures. A discharge from the pin site occurred in 46 per cent of cases. In many cases the discharge was slight, but in 22.5 per cent there was osteomyelitis of the bone and the discharge lasted many months longer than the fracture took to heal; death—the most serious potential complication of the method—occurred in 10 per cent of cases. Most of the longstanding cases and those that were fatal had not been treated initially by application of a plaster cast. Even a plaster cast does not appear entirely to mitigate the risk of infection around the pin site since, when the swelling subsides, the cast may not prevent movement. Although he recognizes the advantages of ambulatory treatment and the early movement of joints, Siris is of the opinion that the danger of infection in the unsupported soft tissues around the pin sites is too serious for pin fixation to be recommended as a routine procedure. When distraction and delayed union occurred in cases treated without a plaster, the causative factors were considered to be ambulation, failure to transfix the fragments, elasticity of the pins, pressure of the pins against the bones and inadequate support of the pins and soft tissues by the use of a too short plaster cast. In order to obtain more rigid fixation in fractures of the tibia and fibula Siris employed, among other procedures, a

transfixation pin across the fracture site, but in no case was sustained impaction and immobility of the fragments obtained without application of a plaster cast. Early removal of the pins so as to prevent sustained distraction and infection is clearly indicated. In the treatment of oblique and spiral fractures of the femur the most satisfactory results were obtained without plaster, but in transverse or comminuted fractures distraction with pins had to be carefully guarded against. It is concluded that external pin fixation with or without plaster is not indicated when a more conservative procedure which gives a good clinical result is available. The pin fixation should be restricted to certain problem fractures and compound fractures with displacement which can be reduced under visual manipulation and can be held in place until a plaster cast will retain the fragments in position.

Basic problems of bone grafting—Murray discusses the basic problems in bone grafting for ununited compound fractures. A bone graft is used to bridge the gap between two bone fragments and its success must depend upon full and permanent incorporation of the graft into the host with much new bone formation into the surrounding tissues. Good functional length and alignment must be obtained and infection must be eliminated. New bone in adults is formed only from undifferentiated connective tissue and needs a local sufficiency of calcium and phosphate obtained through the action of an enzyme, phosphatase, which is most active in an alkaline medium. The amount of new bone formed depends upon the amount of available connective tissue. Its density and permanence depends, first, upon the maintenance of a constant local supply of calcium and phosphate to replace loss by metabolism, secondly upon a favourable hydrogen ion concentration of the tissue fluids, and thirdly upon the stresses and strains to be met. It should be the surgeon's aim to establish those conditions which are favourable for successful grafting. In the author's opinion, the type of graft used is of secondary importance provided certain basic principles are observed. All sources of infection must be eliminated before operation, both generally by the use of chemotherapy and the maintenance of good health and locally by means of adequate drainage of the wound and removal of any sequestra or foreign body. Sufficient time should be allowed for the primary wound to heal and infection to subside before operation is undertaken. A preliminary stage may be necessary to implant new sources of undifferentiated connective tissue and to supplement a deficient local circulation. Exercises must be performed in order to maintain the local circulation and to improve the muscle tone. At operation all scar tissue between the bone ends must be removed so that the graft can be easily vascularized by newly formed undifferentiated tissue. The graft must be fixed rigidly to the host so as to prevent local inflammation and possible resultant failure to form bone. After operation the guard against infection must be maintained and the graft must be kept rigid until there is firm bony union. As soon as possible active and passive exercises should be started for the purpose of maintaining the circulation and good muscle tone.

Reduction

The Masland plan of treatment—Masland criticizes ordinary conservative methods of fracture treatment on the grounds that they often fail to correct deformity or maintain correction and cause atrophy of tissues, retarded healing and persistent joint stiffness. Methods of traction applied to skin and muscle are often mechanically insufficient since the muscles are not always attached to the injured portion of bone but merely enclose it. Bone traction proper often fails because of improper alignment. Masland describes the primary essential of his own plan of treatment as extension between supports placed upon the bones immediately above and below the fractured bone. Splint equipment adaptable to fit all conditions makes extension in the normal line of the bone which is brought to normal length and alignment without side strain. For example, the equipment for dealing with a fracture of the femur consists of an unpadded cast on the leg and foot moulded to all the contours. Embedded in the upper part of the cast are metal plates which have pins on their projecting ends and are set to lie opposite the axis of the knee joint. To these pins and underlapping them, are attached splint arms which project upwards on both sides of the femur, and by means of swivels are attached to the sides of a padded elliptical ring. The ring is made in two pieces for adjustment and forms the support above against the pubic ramus, ischium and iliac wing. The splint arms are enclosed in clampable sleeves. With manual and then screw turn buckle distension the limb is brought to the desired length and then the overlapping arms are clamped. After reduction the pressure is reduced to the patient's comfort. Masland states that and he condemns procedures such as that which uses the Smith Petersen nail. Joint function is preserved throughout his method of treatment.

Bone grafting

Use of chip grafts—Mowlem reports on 75 examples of successful cancellous bone chip grafting for the purpose of restoring contour and continuity in fractures of facial and cranial bones, mandible and tibia. This method reverses the accepted standards of bone grafting but was adopted because fragmentation of the graft provides a larger surface area for ingress of newly formed capillaries and for access of serum to the transplanted bone cells, thus rendering survival more likely. The graft is derived from the ilium owing to that bone's porosity and relatively high cellular content. Fragmentation of the graft not only increases chances of survival of the graft but also simplifies operative technique. Through a 3 inch incision the crest and outer plate of the ilium are freed from muscular and aponeurotic attachments and

a block of bone is removed with an osteotome. The cortex is discarded and the remaining cancellous mass is divided into chips about $1 \times 0.5 \times 0.2$ cubic centimetre. Irregularly shaped chips are useful but if they are too small excessive condensation may occur. In the case of grafting for restoration of contour, wide exposures, bevelling of cranial margins, accurate templates, tedious shaping of one-piece grafts and difficult fixations have all been eliminated. Grafts for restoration of continuity need various methods of bone immobilization. The author stresses that in dealing with long bones, the stripping back of the periosteum, through which nutrient vessels pass, may jeopardize blood supply as may also heat generated by power-driven saws or burrs. The author claims for his method the advantages of simplicity, decreased recovery time and more certain bone regeneration.

Onlay grafts in long bones.—Boyd considers that ununited fractures in long bones are best treated by massive onlay grafts. In 575 cases treated by bone grafting, over 90 per cent of ordinary non-unions obtained bony union after application of a single onlay graft. Any associated infection having been eliminated, the pseudo-arthritis is then excised, the eburnated bony ends of the fragments are freshened or resected and their medullary canals are curetted in order to allow re-establishment of circulation. The cortical portion of a tibial graft is fitted into the prepared graft bed, its location being chosen to allow the graft maximum mechanical advantage and adequate soft tissue covering. It is fixed by non-electrolytic metallic screws, of which there are at least 2 in each fragment and which are long enough to extend through both cortices of the grafted bone. Osteogenic endosteal bone from the tibial graft is packed about the fracture site. For the purpose of obtaining bony union in a congenital pseudo-arthritis, or in difficult cases such as those of non-union near joints, in which screws do not hold well in adjacent osteoporotic bone or in which a bone defect requires bridging, a dual bone graft will be more likely to secure mechanical fixation. By this method, two onlay bone grafts are placed on opposite sides of the grafted bone and are transfixed by screws passing through both grafts and the intervening bone. Among other advantages the dual bone graft acts as a bone clamp compressing the fragments or as forceps to hold a short fragment. Transplantation of a whole fibular graft can successfully bridge large bony defects in radius, ulna or humerus. A fibular graft is not strong enough for this purpose in the tibia, for which a notched fibular graft and a tibial graft are both used, the space between being filled with osteogenic cancellous bone. When the procedure is feasible, the leg can be shortened, thus closing the gap, and a single or dual graft can be applied.

Diet

Nitrogenous intake and protein replacement.—Howard and his colleagues attempt to evaluate the part played by diet on post-traumatic nitrogen deficit in patients convalescent from bone fractures and in patients with osteotomies. Patients of various sizes were standardized in terms of the "average man" who during rest in bed expends the energy of 1,600 calories per day, and in whom 60 grammes of protein or 10 grammes of nitrogen maintain nitrogen equilibrium. When thus fed, healthy vigorous patients showed a negative nitrogen balance. It was noted that fracture patients with a widely varying protein intake exhibited nitrogen losses similar in amount during the period of maximum protein katabolism and that negative nitrogen balances were greater than was expected and were even more marked with higher protein diets. With an intake of 9 more grammes of nitrogen per day, 9 more grammes of nitrogen appear in the urine. Nitrogen equilibrium in fracture cases was not established in all cases until 41–52 days after trauma. In osteotomy cases, nitrogen losses during the height of protein katabolism varied much more widely individually than they did in fracture cases and restoration of nitrogen equilibrium occurred much sooner: 12–20 days after operation. A comparison of 2 cases in which the patients were similar in age, size and body build and had identical osteotomies, and of whom one received in 10 days 50 grammes more nitrogen and 8,000 more calories than did the other, shows total nitrogen losses to be the same, the excess being excreted quantitatively in the urine. The results of the study indicate that in response to trauma a vigorous protein metabolism takes place with losses of large amounts of the nitrogenous portion of body protein and that protein food of extra good quality does not conserve the endogenous protein. Such a reactive process may be of advantage to the patient.

Traction splints

Result of treatment by the Stader splint.—The end results of the treatment of 110 acute fresh fractures by the use of the Stader splint, at the Naval Hospital, Philadelphia, are discussed by Shaar, Kreuz and Jones. Of these patients, 107 were returned to duty or to their previous occupations, 2 were cases of non-union and one patient, who had had multiple fractures of the spine and a compound comminuted fracture of the tibia, was invalided from the service. There were 11 cases of fractured femur, 2 of which were compound: one transverse fracture of the middle third of the shaft resulted in non-union, and in the 10 successful cases the average period of disability was 17 weeks. There were 42 cases of fractures of the tibia and fibula, and one case of non-union; the average period of disability was 24 weeks. The authors had only one case of infection in the series—an abscess, which developed 8 months after the patient had returned to work, at the site of a tibial pin, and which was cleared up by incision. Infection from pins, which must be distinguished from true infection, occurred in 10 per cent of the cases. The authors noted a decrease in the frequency of pin infection since they discouraged early weight-bearing. Pin sequestra occurred in 3 cases: one pin was excised, one

was discharged spontaneously and the third was absorbed without infection. In the 2 cases of non-union Shaar and his colleagues consider that there may have been too firm an apposition at the fracture site, grafting was subsequently successful in these cases. The authors note that 2 cases of bowing occurred after removal of the splint when radiology had shown that there was apparent firm union. They suggest that this may have been due to the maintenance of a reduction so rigid that the functional stimulation of slight movement was absent. With the use of a new adaptation of the splint, to be used as a routine in transverse fractures, it is hoped to avoid this complication.

Methods of splinting

Cellulose rayon and cellulose acetate—Kulowski, French and Erickson introduce a new plastic medium for clinical immobilization. The "starched apparatus" introduced in 1834 was displaced in 1852 by plaster of Paris which has since remained the popular medium for immobilization. Its advantages have been so great that its disadvantages have been overlooked. It is heavy, has poor penetration for x-rays and has poor resistance to absorption of moisture and it irritates the skin. The new medium, Aire-Lite, is composed of a plastic fabrication in the form of a dry open-meshed flexible bandage which can be applied to any part of the body and is then sprayed with a volatile setting liquid in order to form a rigid structure. The bandage is knitted from a mixture of cellulose acetate and a regenerated cellulose rayon. It is then processed so as to control shrinkage and the setting and drying qualities. The spray consists of volatile liquids with acetone as an active ingredient. The medium is light in weight, resistant to moisture, has good penetration for x-rays and is comfortable to wear. The authors analyse the results of its application in 136 patients, including 43 simple and 43 compound fractures. In 22 cases Aire-Lite was used in primary fixation, and in 64 fractures of which 42 were compound—31 of them being severe—it was used subsequently to plaster or other fixation method with good results. Pathological conditions treated include haematogenous pyogenic osteomyelitis, tuberculosis, arthritis and osteochondritis. The majority of these were treated primarily with Aire-Lite. Splints of wood or wire can be incorporated in the medium in order to give greater strength when required. The medium can be applied in the form of stockinette, splint or bandage. One drawback is shrinkage causing constriction and this must be guarded against for the first 24 hours after application, especially to hand or forearm. Aire Lite takes longer to set than does plaster.

Regional

Clavicle

Use of plaster cast—Packer describes a simple method for the treatment of fractured clavicle based on the injection of a local anaesthetic into the fracture site, the reduction of the fracture by manipulation of the fragments and general positioning of the shoulders and the maintenance of the reduction by immobilization in a light plaster cast. The treatment permits complete freedom of both arms and, applied to soldiers, allows of the wearing of uniform and limited service during treatment. The limitations of other methods of conservative treatment are discussed. Complete rest in bed with sand-bag immobilization may be necessary for fractures complicated by shock and other injuries but its use in uncomplicated cases, either as a single method of treatment or followed by the use of clavicular cross, produces discomfort, frequent readjustments and increase in the need for general nursing. The figure-of-eight dressing with or without a pressure pad is applicable to green-stick fractures or incomplete fractures but is unsatisfactory in patients confined to bed. In ambulatory cases it may produce circulatory and nerve disturbances from pressure under the armpits. Frequent readjustments are again a disadvantage. The Sayre tape dressing and Velpeau bandage often produce skin rash, incomplete immobilization and inability of the patient to dress himself. After trying various types of plaster cast, Packer found that the best result was given by a felt pressure pad over the proximal fragment encased in a jacket extending down to the lower ribs, closely applied to the root of the neck and well out to both deltoid muscles anteriorly. Backward pressure is exerted by the cast on the shoulders and forward pressure is against the spine. The plaster is trimmed from under the armpits in order to allow the limbs to hang normally. The cast is left in place for 6 weeks. Painful crepitations during respiration do not occur when the cast is applied snugly.

Rupture of supraspinatus tendon

Method of operative repair—Jones discusses a simple operative repair for complete rupture of the supraspinatus tendon and gives clinical details of 3 cases. The condition must be relatively common since it is found at necropsy in 15–20 per cent of all patients over 30 years of age. Clinically, however, the condition often remains undiagnosed, a painful shoulder being treated conservatively for years without improvement. After rupture has occurred, nature's ineffectual attempts to repair the damage result in the formation of much connective tissue and deposition of calcium, the area becoming the site of a chronic subacromial bursitis, other possible sequelae are arthritis of the shoulder joint and rupture of the long biceps tendon. Contrary to the general belief the author states that it is not a self-limiting condition of 2 years' duration, occurring only after 30 years of age, since he has had cases with histories of up to 17 years' duration, one case is cited in which the lesion occurred in a girl of only 19 years of age. Jones advises exploration of the joint in all cases of chronic pain which have not responded to treatment, and the use of the Cubbins transacromial-clavicular incision which has the merit of giving adequate exposure without fear of injury to the circumflex

nerve, by splitting the deltoid muscle. In the author's method of repair substitution flaps from the adjacent infraspinatus and subscapularis muscles are used, so that capsular continuity is restored; there is much improved movement and relief from pain as a result.

Wrist joint

Fractures of the carpal scaphoid bone.—Hambly draws attention to the commonness of fractures of the carpal scaphoid bone and to the severe consequences of inadequate treatment. All sprains and suspected fractures of the wrist should therefore be submitted to x-ray examination in 3 planes, of which the oblique plane test shows a fracture of the carpal scaphoid bone. Often a recent fracture does not show in any skiagram but if clinical tests suggest a fracture, the appropriate treatment should be instituted. If a fracture exists, decalcification of the fracture edges can be recognized after 3 weeks. All fractures must be immobilized in plaster for 12 weeks or until full bony union is confirmed by two sets of skiagrams of the 3 views taken at intervals of 3 weeks. There is no clinical proof of union. In plaster the wrist should be in 30° of dorsiflexion and the thumb in true anatomical abduction, that is, pointing to the floor when the palm is held horizontally. Reapplication of the plaster is necessary after 2 weeks. Fractures of the wrist and proximal pole may require up to 12 months of immobilization. The tubercle is extra-articular and a fracture of it unites with a maximum of 3 weeks in plaster. An important factor in non-union is that in about one-third of the total number of scaphoid bones the proximal pole and proximal one-third of the bone possess little or no blood supply. Avascular necrosis occurs after fracture together with osteoarthritis of both the carpal bones and the wrist joint, and requires treatment by early excision of the proximal fragment. Osteoarthritis, if severe, necessitates arthrodesis. Drilling is preferable to grafting in the treatment of established non-union, shown on the skiagram by considerable sclerosis of the cystic cavity between the fragments which display increased density. If few symptoms exist, however, Hambly thinks that no treatment is indicated.

Ankle joint

Treatment of Pott's fracture.—Todd defines Pott's fracture as the name given to a group of fractures around the ankle joint which are caused by forcible abduction of the foot, and discusses its treatment. In order to aid diagnosis x-ray pictures should always be taken, as clinically a Pott's fracture may be mistaken for a sprain, although in the latter the point of maximum tenderness is over one or other of the lateral ligaments whereas in a Pott's fracture maximum tenderness is over the fibula 3 inches higher. The author advises complete and immediate reduction of both bony and soft tissues. If reduction is delayed for any length of time, muscular contractions and oedema of the tissues complicate the position and severe disability may result for which conservative treatment does not give any cure. Anaesthesia for the purpose of obtaining complete muscular relaxation should always be employed and afterwards a further x-ray examination should always be made in order to test complete reduction. If the procedure is successful the outer edge of the tibial shaft should be in line with that of the talus and the upper edge of the talus horizontal and at right angles to the shaft of the tibia. A lateral x-ray examination should eliminate the possibility of backward displacement and equinus. There is never any possibility of gradual adaptation of the tissues to compensate for incomplete reduction of the fracture and late attempts to restore alignment of the ankle joint are useless. The "mechanical arthritis" which develops after malunion may cause a crippling disability which can be relieved by arthrodesis of the ankle joint; a painless foot with fair walking capacity is the result.

Fractures of femur

Importance of delayed primary suture.—In treating compound fractures of the femur in 70 battle casualties, Burns and Young report that they soon became convinced that delayed primary suture gave the best chance of early healing and avoidance of bone infection, since the use of penicillin had eliminated the danger of spreading sepsis. On arrival—usually several days after having been wounded, having had debridement and immobilization in Tobruk plasters carried out by forward surgeons, and having been given varying amounts of penicillin in transit—each patient received 20,000 units of penicillin intramuscularly 3-hourly for 5 days. Twenty-four hours after arrival, the patients' wounds were inspected and swabs were taken; only 2 gave cultures of streptococci and of *Staphylococcus aureus*. The clinical appearances, not the bacteriological findings, determined the extent of suturing then undertaken. Owing to oedema, some wounds were partially sutured then and completed some days later. Any pus present, being due to Gram negative organisms, was considered to be relatively innocuous. Drainage, even by penicillin tubes, was considered to be undesirable. Loculation of pus occurred in only 6 unsutured wounds. Only 4 of the 48 wounds which had been completely sutured had a sinus at 3 months, against 9 of the 22 incompletely closed. In 62 cases, the average time of bone union was 13 weeks. The maximum shortening in cases treated with below-knee pin-traction was half an inch, except in one case in which bone fragments were inadvisably removed. Early knee movements, in order to prevent adhesions, were employed in 58 cases. Of these, judging by the range of movements present at 4 months, 40–50 are expected to have full restoration of function within 9 months.

Foot

March fractures (pathological fracture).—The common picture seen in fractures of the foot is immediate loss of function as a result of some sudden or direct violence. In the variety known as march fracture there is often only mild discomfort although the condition may be

disabling Bernstein and Stone give a report of over 300 cases and describe a new method of treatment. They believe that the fracture is due to direct bone stress after exhaustion of muscles, ligaments and fascia, in which the long march is a definite aetiological factor. The first complaint is of pain during a march, which gradually, after days or weeks, leads to a limp. Later, swelling of the dorsum of the foot occurs. The foot is held rigidly, either inverted or everted according to the metatarsal fractured. The most constant finding is localized tenderness at the fracture site. Early roentgenograms may be negative or, viewed with a magnifying lens, may show a hairline fracture involving only the cortex of a metatarsal shaft. Later more definite fracture lines or callus may be seen, the latter increasing with time. Although the fracture is usually incomplete at first it may later become complete by continued weight-bearing. Patients with a march fracture complain of pain during the push-off phase of the gait. The pain is markedly decreased if the foot is held rigid and movement at the metatarsophalangeal joints is eliminated. The authors therefore recommend the fitting of a countersunk steel bar about $\frac{1}{2}$ inch wide, $\frac{1}{4}$ inch thick and 6 inches long in the sole of the shoe on the underside or non weight bearing surface. The relief obtained is very noticeable and the patient is usually able to continue training until the fracture heals after 4-5 weeks. The disadvantages of immobilization in plaster do not occur and subsequent physiotherapy is not necessary.

Mandible

Use of cap splintage—Penn describes the modern treatment of fractured jaws. Many factors have to be considered: type of fracture, type of jaw, time lapse before treatment, presence of complications and apparatus available. Efficient first aid demands only support of the mandible from below against the maxilla by an ordinary crepe bandage. The fractured jaw may be immobilized by means of the eyelet type or arch type of wiring and fixing the mandible. Wiring methods are suitable only as temporary measures because they cause pain, loosen teeth or set up gingivitis if they are used for any length of time. The commonest effective method for permanent fixation is cap splintage. Plaster impressions of both jaws are taken, often by sections, and to these are fitted cap splints cast in metal which are afterwards fitted to the teeth on the separate fragments, these being brought together by elastic traction or wiring. When in position the two jaws are immobilized by one or more precision locks and a screw connecting-bar between the fragments. The Gunning splint for fracture in good position in an edentulous jaw makes use of the patient's own denture combined with bandaging. Extra oral mandibular splinting is developing along the lines of the Rodger-Anderson method of splinting long bones by placing cross pins into each fragment and locking them together by universal joints or cross bars. Except in skilled hands this method is not without danger to soft tissues. The Brenthurst clamp splint has a powerful grip on the inferior border of the mandible and may be useful in those cases which are unsuited for the cap splint. Secondary infection causing malunion or delayed union may ensue after a compound fracture, especially if a tooth is in the line of the fracture, but it can be cleared up rapidly by means of penicillin lavage.

Maxilla and mandible

Treatment—Coakley and Baker analyse 212 cases of jaw fracture. To delayed fixation they attribute much infection. Owing to discharge from hospital and failure of follow-up, the total period of immobilization was difficult to ascertain. They report 2 cases of 4 fractures of 212 cases within 18 months there were 16 fractured maxillae as compared with 3 per 1,000 in Dunning's 1,065 series of cases which occurred between 1906 and 1913. The authors emphasize the increase in the number of motor accidents, which are the cause of 16.5 per cent of the 212 cases. Seventy-two per cent of the series were compound fractures with consequent complications. In 47 per cent the authors left teeth in the line of fracture intact until the postfixation period, in this group the incidence of infection was 62 per cent whereas after immediate dental extraction infection occurred in only 22 per cent. In all cases the most simple form of fixation was used and when teeth were present and available intermaxillary wiring was used. Amongst 9 edentulous cases circumferential wiring was used in 6, Gunning splint in one, Barton bandage in one and in one case of edentulous maxilla fracture there was no treatment. In 6 out of 11 cases in which posterior reduction with wire in the posterior fragment and plastic head-cap were used, non union or poor position of fragments or infection led to unsatisfactory results and this method has been abandoned. Compound block in order to hold the posterior fragment in position, especially if it were used immediately before any overriding was present, gave good results. Interosseous wiring was successful in 3 cases of non union. Fractured maxillae were treated with Kingsley splints or the Major appliance if the use of simple interdental wiring was not indicated. Kirschner wire fixation has proved to be satisfactory.

Fractures of spine

Shovellers' fracture—Annan describes 8 cases of fracture of the spinous process of the seventh, or sixth and seventh, cervical vertebrae occurring in prisoners of war who were employed in shovelling sand or soil. The fracture occurs about the middle of the process at right angles to its long axis and there is usually separation of the fragments with downward displacement of the detached fragment. Crepitus and movement can be elicited when the ligamentum nuchae is relaxed. Conservative treatment only is required for recovery and

there is no indication for surgical removal of the fragment. In the cases described there were possible predisposing factors such as muscular fatigue and poor nutrition but the circumstances precluded any detailed investigation of diet. The cause of the fracture is indirect violence from muscular pull and there is usually a premonitory phase of pain in the back before the actual snap. Shovelling is undoubtedly the precipitating cause. The ligamentum nuchae is attached to the spinous processes of the sixth and seventh cervical vertebrae and continues towards the occiput with a fibrous sheet connecting it to the spines of the other cervical vertebrae. In a stooping position this ligament is taut and on account of its continuation caudally with the ligament connecting the spines of the dorsal vertebrae it exerts a compressing force on the prominent spinous processes. The strain of lifting the shovel is transmitted through the muscles fixing the left scapula to their origins in the seventh or sixth spinous process. When the strain is constantly repeated, avulsion of the spinous process may occur.

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DIVERTICULOSIS AND DIVERTICULITIS

See also B.E.M.P., Vol. IV, p. 207; and Cumulative Supplement, Key No. 355.

Introduction and definition

X-ray appearance

Radiographical records.—Diverticulitis, as defined by Henderson, is an inflammation of diverticula of the colon with or without involvement of the adjacent bowel wall and peritoneum. This process, if recurrent, produces a weakening and devitalizing effect on the tissues involved and progresses to a diverticulosis, a condition in which the mucosa is forced, in the form of herniated sacs, through the bowel wall at points at which it is weakened by the passage of lymph and blood vessels. The devitalizing effect of chronic constipation produces similar results. Carcinoma and polypi, too, seem to produce some local weakening of the colon musculature and give rise to a diverticulosis which is often demonstrable radiographically some time before the growth itself is. Diverticula occur singly or in numbers, locally or throughout the entire colon, and their development may be divided radiographically into five stages as follows. (1) The ripple edge border. This is really a localized colitis in which the wall of the affected area is in a permanently spastic state. Such areas are the precursors of herniated sacs. Even if resolution occurs at this stage considerable fibrosis of the wall of the colon may persist. (2) Palisading. This shows as small but definite projections. (3) As the lesion progresses, pulsion diverticula appear. These are small sacs, still possessing free movement, which are seen to protrude from and retract within the wall. (4) Retractable ballooning. This shows sizable diverticula which balloon out on inflation and collapse on deflation. (5) Permanent diverticula, fibrosed and persistently distended, appear outside the bowel wall. Up to the third stage and in some cases in the fourth stage the prognosis is good and the prospects of successful treatment are hopeful, but once the stage of permanent diverticula has been reached a measure of relief is all that can be hoped for.

Henderson, N. P. (1944) *Brit. J. Radiol.*, 17, 197.

DRUG ADDICTION

See also B.E.M.P., Vol. IV, p. 246; and Cumulative Supplement, Key No. 359.

Treatment

Curative

Intensities of abstinence syndromes.—Andrews and Himmelsbach examine data on the intensities of abstinence syndromes in 127 morphine addicts. The minimal amount of morphine sulphate required to prevent signs of abstinence ranges from 40 to 500 milligrams per diem. Mathematical analysis indicates that a functional relation exists between these stabilizing doses and the syndrome of total abstinence for 7 days. It is revealed by the curve plotted to denote the relation that the signs and symptoms of total abstinence attain the maximum severity with a daily dose of about 500 milligrams and that greater doses have little additional

effect. Theoretically, greater imbalance of the autonomic nervous system results from small early doses. At first the drug is highly effective in small quantities but as addiction proceeds the added amounts become less potent. Finally the addict must become reconciled to a state of maximum dependence with an almost complete loss of the satisfaction originally obtained. Since 1935 the patients under review have required progressively smaller stabilization doses of morphine and the more recent abstinence syndromes have been less severe. This may be correlated with the difficulty now experienced by morphine addicts in obtaining large quantities of illicit drugs and with the comparatively poor quality of these opiates.

Andrews, H. L., and Himmelsbach, C. K. (1944) *J. Pharmacol.*, 81, 288.

DRUG ERUPTIONS

See also B E M P, Vol IV, p 261, and Cumulative Supplement, Key No 360

Types of drug eruptions

Sulphonamides

Sensitization of skin after inhalation of sulphonamide powder—Peterkin discusses the incidence of dermatitis after local application of sulphonamides in a series of 65 cases in the North African war zone. All the patients had had local treatment with sulphonamides, generally given in powder form for minor skin lesions, and many had been admitted to hospital with a diagnosis of spreading impetigo for which more sulphonamides had been given. Mild reaction to sulphonamides was characterized by a maroon erythematopapular rash, but if the reaction was severe the face became oedematous and crusted and there was associated photophobia, cheilitis, glossitis, stomatitis and rawness of scrotal skin. The eruption might then spread to exposed areas of skin and there was often toxæmia. When healing began the condition resembled an impetiginized seborrhoeic dermatitis and later when the crusts were shed the picture was akin to that of ariboflavinosis. All cases showed a slight to moderate polymorphonuclear leucocytosis. The author believes that sensitization of the skin was the result of inhalation of sulphonamide powder. He treated 91 cases of impetigo and 93 cases of impetiginized seborrhoeic dermatitis with 5 per cent sulphathiazole in Lassar's paste or in water-miscible creams and had only a mild reaction in one case, which suggests that the above may be the best method of treatment of skin lesions with sulphonamides. Patients were desensitized to light by gradual exposure of the skin to sunlight, protected by 10 per cent tannic acid in tragacanth or Lanette wax SX cream. Continued observation was difficult, but most patients in the series were discharged able to tolerate the Mediterranean sun. Peterkin ends by urging that sulphonamide powders should not be used for the treatment of minor skin lesions.

Common drug eruptions

Sulphonamides

Prevention and treatment—Tate and Klorfajn discuss the prevention and treatment of sulphonamide dermatitis. Originally, large oral doses in spite of the resulting eczema was the method of desensitization advised. It was found, however, that in each patient there was a threshold dose below which no reaction occurred, and that doses just above this produced only slight reactions. The authors therefore concluded that a dose between the threshold dose and that producing a maximal reaction would cause desensitization if treatment were prolonged for a sufficient period. Tate and Klorfajn have used this method successfully in 30 cases. A test dose of 0.125 gramme of sulphonamide is given. If the reaction is severe the dose is reduced, if only moderate symptoms ensue the dose is continued twice daily until the resulting reaction has disappeared, the dose is then doubled and the same procedure is followed. When the increment fails to produce a reaction a test dose for sensitization is given—2 grammes followed by 2 doses of 1 gramme each, at 4-hour intervals. If this dose produces a reaction the prior dose is increased and the patient is retested when the skin is clear. If reaction does not occur treatment with the prior dose is continued for 14 days. Assuming that desensitization results from neutralization of the antibodies, the authors state that it should be possible, by oral administration of the drug, to prevent sensitization by using up the antibody as fast as it is formed. They describe two cases in which the patients proved to be susceptible to sensitization and in which the drug was orally administered and locally applied with impunity. Tate and Klorfajn consider that an oral dose of 0.25 gramme twice daily is usually an adequate preventive dose, but it should be continued for 14 days after local application has been stopped.

Peterkin, G. A. G. (1945) *Brit. J. Derm.*, 57, 1.

Tate, B. C., and Klorfajn, I. (1944) *Lancet*, 2, 553.

DYSENTERY, BACILLARY

See also B E M P, Vol IV, p 317, and Cumulative Supplement, Key No 364

Treatment

General treatment

Difficulties in eradication of bacillary dysentery—Fairbrother propounds the problems involved in control of bacillary dysentery and states that "the eradication of the disease from this country [Great Britain] requires the detection and treatment of all carriers of *Bact. dysenteriae*". On 245 occasions *Shigella dysenteriae* was isolated from the faeces of 2,500 Italian prisoners in Great Britain who showed no clinical indications of infection although all gave a history of dysentery or enteric fever during the previous 3 or 4 years. The types

isolated were Flexner (170), Shiga (57), Schmitz (11) and Sonne (7). Investigation has suggested that at least 12 successive daily negative results are essential before an individual can be pronounced to be clear of infection and tests should be delayed for at least 6 days after cessation of sulphonamide treatment. The author emphasizes the intermittency of excretion and the fact that many carriers have never displayed any symptoms. Tests of treatment of Sonne infection with sulphaguanidine and succinylsulphathiazole suggested that these drugs have a good clinical but a disappointing bacteriological effect, and 2 persistent carriers continued to excrete Sonne bacteria for 9 months despite repeated courses of both drugs. The sulphonamides have, however, proved to be valuable in clearing all except Sonne dysenteries. Succinylsulphathiazole inhibited action of both Flexner and Sonne strains but sulphaguanidine proved to be relatively ineffective. The author condemns the older media, such as MacConkey's, as valueless in investigating suspected convalescent or symptomless carriers and advocates very selective media like desoxycholate citrate. A large influx of carriers on return of men from foreign service may be anticipated, and Fairbrother stresses the importance of adopting a long-term policy towards this danger. Restricted laboratory facilities, the trivial nature of symptoms in many cases and consequent failure to report sick, and the difficulty in enforcing measures of personal hygiene and sanitation are great obstacles which will be encountered in any attempt to adopt such a policy.

Sonne dysentery and sulphanilylbenzamide and sulphanilylamidobenzamide.—Swyer and Yang report the results of the use of sulphanilylbenzamide and sulphanilylamidobenzamide in the treatment of the Sonne type of dysentery. No toxic symptoms were observed apart from slight anorexia. In each course the total dosage was 6 grammes for each stone of body weight. For patients weighing over 7 stone the complete dose was 44 grammes. Sulphanilylbenzamide was given to 41 patients and the stools became normal within 48 hours. Temporary bacteriological relapses occurred in only 3 cases. The results were almost equally satisfactory in 71 patients treated with sulphanilylamidobenzamide and, with the exception of 11 temporary relapses, bacteriological clearance occurred in an average time of 3.6 days. It was interesting to note that, in 30 cases treated with half the original dose of sulphanilylamidobenzamide, both the average time of clearance and the number of relapses were less. Furthermore, the blood concentration was almost as great as it was with the full dose. There were 24 relapses in the complete series of 142 cases. Failure to achieve initial success was attributed either to intermittency of bacterial excretion or to reinfection. For comparison with the other two compounds succinylsulphathiazole (Sulphasuxidine) was administered to 26 patients. With this drug there was not a great improvement in the stools, but the bacteria disappeared in an average time of 2.4 days. The relapse rate was 34.6 per cent. Comparative tests with sulphanilylguanidine (sulphaguanidine) showed that the two drugs under investigation reached a higher concentration in the blood. The concentration of sulphanilylbenzamide was 4 times that of sulphanilylguanidine.

Fairbrother, R. W. (1944) *Brit. med. J.*, 2, 489.

Swyer, R., and Yang, R. K. W. (1945) *Brit. med. J.*, 1, 149.

DYSMENORRHOEA

See also B.E.M.P., Vol. IV, p. 353; and Cumulative Supplement, Key No. 367.

Aetiology

Psychoneurotic considerations

An organ neurosis?—Wengraf defines functional dysmenorrhoea as a symptom complex, often neurotic, associated with menstruation, affecting not only the pelvic organs but the total personality. The psychodynamic aspect is partially explained by reference to the concept of a psychomotor reflex, comprising any particular emotion plus the specific bodily reaction provoked. Neurotics, who have vivid association, may disturb a "normal" psychomotor reflex or establish an abnormal one by connecting old experiences with certain facts or vice versa. Thus menstruation may be connected with past experiences. Emotions primarily belonging to this suppressed material are attributed to menstruation which, as a dysmenorrhoeic girl's history frequently discloses, becomes the realization of old guilt feelings, often connected with hostile feelings against the mother. A panic reaction to the menarche is common; the girl experiences anxiety because she is subconsciously reminded of old traumas such as domestic unhappiness or sexual experiences in childhood, but she associates this anxiety with menstruation. Dysmenorrhoea and its concomitants show the characteristics of an organ neurosis, namely (1) absence of an underlying pathological anatomical process, (2) inconsistency of pain, corresponding to varying affective situations, (3) reversibility, the original normal function being sometimes recovered, and (4) amenability on occasion to various drugs and to suggestion. Psychotherapy may elucidate multiple connections between dysmenorrhoea and the patient's other neurotic symptoms. Dysmenorrhoea may manifest (1) locally in the form of cramps and disturbances of urination and defaecation, (2) generally in the form of anorexia, headache or cardiac disturbances or (3) in the psychosexual sphere as anxiety craving or alteration in libido. Two case reports exemplify Wengraf's theory that as a psychosomatic entity dysmenorrhoea is understandable if the psychic mechanism can be explained by careful elucidation of the history. In another case, dysmenorrhoea was replaced by other neurotic symptoms, originating from the persisting underlying psychic energy. Dysmenorrhoea existing since the menarche is more resistant to psychotherapy which, as another case

report illustrates, may be effective in secondary dysmenorrhoea due to more superficial psychological conflict, for example that which ensues after miscarriage

Treatment

Surgical measures

Phaneuf discusses the surgical procedures used in treating dysmenorrhoea for which conservative therapy has failed. Thorough dilatation of the cervix will often relieve primary dysmenorrhoea. Presacral neurectomy or resection of the superior hypogastric plexus, although often strikingly effective, should be reserved for the spastic uterine form of dysmenorrhoea, when all other methods have failed to relieve the severe cramps. At the same time, a retroposed uterus can be corrected by suspension. The operative procedures of the generative and adjacent organs, diseases of which cause secondary dysmenorrhoea, are considered. Thus removal of myomata causing irregular uterine contractions, excision of endometrial polypi and ablation of cystic ovaries may be responsible for cessation of menstrual pain. Endometriosis of the external variety requires removal of the affected ovaries. Salpingo-oophorectomy, unilateral or bilateral, may be required for endometriosis and for chronic inflammatory disease such as adhesions, chronic pyosalpinx and hydrosalpinx, combined with hysterectomy, it is necessary for carcinoma of the body of the uterus. Hysterectomy, fundic, total or subtotal, possibly combined with ablation of the adnexa, may be necessary for uterine myomata and adenomyosis or for internal endometriosis. All the above procedures bring about cessation of menstruation. Pain due to mechanical disturbances occurring in a retrocaecal or distorted appendix may be ameliorated by appendicectomy or lysis of appendicular adhesions causing distortion. Attention to ureteric lesions and to diseases of the pelvic colon and rectum are other measures sometimes secondarily effecting improvement or cure of dysmenorrhoea. Curettage and a dose of 200-250 milligram hours of radium may benefit membranous dysmenorrhoea.

Phaneuf, L. E. (1944) *New Engl J Med*, 231, 872

Wengraf, F. (1944) *Amer J Obstet Gynec*, 48, 475

EAR DISEASES

See also B E M P, Vol IV, p 402, and Cumulative Supplement, Key Nos 374-384

Acute otitis media

Treatment

Penicillin in acute otitis media and mastoiditis—Ball reports on the treatment with penicillin of 12 cases of otitis media complicating scarlet fever and 5 cases of acute non-scarlatinal otitis media with complicating mastoiditis. Owing to difficulties encountered in obtaining penicillin most experimental work on its use in otolaryngeal disease has been restricted to its local use. In 12 cases of acute scarlatinal otitis media, all with a thick purulent offensive discharge and occasional granulations presenting through a perforation of the tympanum, culture showed a growth of predominating *Streptococcus pyogenes*. In each case sulphadiazine was given for a period of 1-3 weeks and when improvement was observed or suppuration became worse night, was started. In 10 of the 12 cases there was rapid recovery, resolution of the tympanum units. In the other 2 cases, one gave a history of recurrent suppurative otitis and, after a discharge but a patent perforation remained. The second patient had a previous history of labyrinthitis supervened, surgical intervention had been begun symptoms of left formed. The total dosage of penicillin was 2,000,000 Oxford units given over a period of 12 days. Two weeks after mastoidectomy there were still symptoms of slight labyrinthine inflammation. In 5 other cases of non-scarlatinal otitis media with complicating mastoiditis cultures in 4 yielded *Staphylococcus aureus* and haemolytic *Staph aureus* was found in the remaining one. Treatment with 460,000-2,000,000 units of penicillin after sulphadiazine therapy had failed resulted in cure in from 3-18 days. The author remarks that although this series is too small to justify any clear conclusion, the prompt response to treatment is promising.

Ball, S. (1945) *Arch Otolaryng*, Chicago, 41, 109

ECZEMA

See also B E M P, Vol IV, p 447

Clinical picture

Special eruptions to which the name, eczema, has been given

Varicose eczema—Smith describes vesicular skin eruptions secondary to longstanding ulceration, the latter usually being in the leg and of varicose origin. The original ulcerated patch suddenly becomes red, painful and sharply inflamed, and broken-down tissue products are absorbed into the blood stream, which cause a skin reaction of acute type on the flexor aspects of the forearms, on the neck and on the trunk. These erupt from above downwards, start first as papules and later change to vesicles. At the same time vesicles erupt about the primary patch. Owing to the chronicity of the ulcer, or because of bad treatment, the patient becomes sensitized to his own exudate, and a condition of eczema autolytica arises, this being a non microbic infection affecting uncovered areas first. It is advisable always to examine

the whole cutaneous surface, otherwise the small chronic leg ulcer may be missed and the condition wrongly diagnosed. The condition does not occur with acute or subacute extensive dermatitis, being associated only with small and chronic ulceration. Treatment is directed to the primary ulceration, which must heal before the secondary eruption will subside. The patient is put to bed, and the bed is raised at the foot for the purpose of accelerating venous return. Boric acid fomentations or hypertonic saline compresses are applied every 4 hours for 3 days, followed by the application of an iodine and starch paste and firm bandages. In order to relieve itching and promote sleep small doses of phenobarbitone and bromide are useful. The condition has become more common during the war in people with a stubborn primary focus of ulceration because they have had to stand for long hours at their work.

Kaposi's varicelliform eruption.—Lane and Herold state that Kaposi's varicelliform eruption may occur as a complication of disseminated neurodermatitis. The authors describe 5 cases in which the clinical course was characterized by a sudden onset of fever, anorexia, malaise and severe cervical adenitis. A herpetiform vesicular and bullous eruption began within 48 hours after the acute onset and continued to develop during the next 5–10 days. The lesions appeared usually on the neck and then spread to the eczematous areas on the face, chest and extremities. The fever declined gradually and the cutaneous lesions disappeared within 8–14 days from the onset. There was no residual scarring from the varicelliform eruption. It was observed that the complication had produced a temporary improvement in the neurodermatitis. The treatment consisted of the use of boric acid packs, oily packs, bland ointments, salicylates and sedation. Administration of sulphadiazine and sulphanilamide were without benefit. The presence of a leucopenia indicated caution in the administration of sulphonamides. Tests on animals proved that the eruptions were probably due to a strain of the virus of herpes simplex, and mouse protection tests showed that the serums of the patients had increasing titres of antibody to this virus. There was no evidence that the causal organism was related to the virus of vaccinia. Moreover, in no case was there a history of recent contact with vaccinia, varicella or variola. Kaposi's varicelliform eruption is unique and deserves to maintain its identity as a separate disease from eczema vaccinatum.

Treatment

Lotions and ointments

Coal tar and its uses.—Davies discusses the modern treatment of eczema. The disease is defined as an itching eruption composed of oedematous papules and vesicles, scattered or aggregated into ill-defined plaques, the main anatomical changes being the collection of fluid between the cells of the epidermis. Idiopathic eczema must not be confused with eczematoid dermatitis caused by external irritants, or with eruptions due to multiple sensitization. Chronic flexural prurigo, which begins in infancy as facial eczema and is inherited as a simple dominant along with tendencies towards hay fever, asthma and migraine, is best treated by prevention of scratching, protection from outside irritants, a normal and sufficient diet and judicious use of crude coal tar. White's tar ointment is useful in all kinds of idiopathic eczema and consists of 1 part each of crude coal tar and zinc oxide, and 8 parts each of yellow soft paraffin and starch. The existing lesions are often easily cured but there are no known means of preventing a recurrence. In acute weeping eczema evaporating wet dressings of 1 per cent aluminium acetate or dilute lead lotion are useful at first, with later calamine lotion and White's tar ointment. Cheirpompholyx, a constitutional and familial disease, if severe may be treated with soaks of solution of coal tar, 1 fluid ounce to half a gallon of hot water. Dangerous and strong applications should not be used, and above all the benzocaine antipruritics and the sulphonamides must be avoided; the former sooner or later produce disconcerting local sensitization and the latter incurable sensitization to sulphonamides and even to light.

Davies, J. H. T. (1944) *Med. Pr.*, 212, 406.

Lane, C. W., and Herold, W. C. (1944) *Arch. Derm. Syph.*, N.Y., 50, 396.

Smith, S. W. (1945) *Brit. med. J.*, 1, 628.

EMBOLISM, ARTERIAL

Treatment

Dicoumarin

Gefter, Kramer and Reinhold report on treatment with Dicoumarol (dicoumarin) of 30 patients with various thrombo-embolic diseases, of whom 25 each received 300 milligrams orally for 2 days and 50 milligrams daily thereafter; 5 received each 200 milligrams every other day. Average predosage levels were: plasma prothrombin, 80 per cent; clotting time, 4 minutes; bleeding time, 2 minutes. On the first dosage schedule, the mean plasma prothrombin fell rapidly to 25 per cent in 3 days, was 20 per cent or less from the fourth to the ninth day, then rose slowly to 50 per cent in 4 weeks and maintained that level. The clotting time increased to 6 minutes in 3 days, remained at this level for 3–10 days, then fell slowly in 4 weeks to a level slightly above the normal. Bleeding time was uninfluenced. Twenty-three patients recovered and 7 died. Haemorrhage, the sole manifestation of toxicity, occurred in 5 patients who all recovered after withdrawal of Dicoumarol. Rectal bleeding occurred on the twelfth day in one patient whose prothrombin was then 11 per cent. In another an episcleral haemorrhage developed on the sixth day, when prothrombin was 8 per cent. One woman, who had vaginal bleeding and haematuria on the eighth day after Caesarean section, when

prothrombin was 8 per cent and clotting time 10 minutes, required one blood transfusion. Changes were not observed in leucocyte counts, haemoglobin, blood sugar, blood urea, icterus index or urinary composition, which were determined frequently in many patients. Improvement in peripheral vascular circulation was demonstrated by oscillometer and the histamine test in 6 of 8 cases. The authors conclude that the only reliable method of ascertaining the correct Dicoumarol dosage, in order to avoid the marked rise of haemorrhage when prothrombin falls to 20 per cent or less, is by making frequent plasma prothrombin determinations.

Gefter, W I, Kramer, D W, and Reinhold, J G (1944) *Amer Heart J*, 28, 321

EMPHYSEMA OF THE LUNGS

See also B E M P, Vol IV, p 508

Surgical emphysema

Course and prognosis

Macklin and Macklin review the conditions in which air may find its way into the pulmonary interstitial tissues. There may be (1) an atelectasis of some part of the lung, followed by hyperinflation in the same or opposite lung, (2) a general overinflation with or without increased intra alveolar pressure and (3) a decreased blood supply to the pulmonary vessels associated with increased intra alveolar pressure or hyperinflation. In all cases the air escapes through ruptured alveolar bases into the sheaths of the pulmonary vessels. It then makes its way along the vessel sheaths to the mediastinum and there presses upon the large vessels at the base of the heart. It may travel into the neck, face, axillae, chest and arms, causing subcutaneous emphysema, or along the aorta and oesophagus into the retroperitoneum, rupturing into the peritoneal cavity. If it goes forward over the heart it may give rise to Hamman's sign, a crunching sound with each heart beat. Other routes are, laterally into the vessel sheaths of the other lung and by rupture through the mediastinal wall, when pneumothorax is produced. Apart from the more obvious indications of its presence the air may cause pain, dyspnoea and cyanosis. Bubbles of air which press upon the pulmonary vessels lead to venous stasis and cyanosis and the splinting action of the air in the connective tissues of the lung prevents the escape of air in expiration and causes dyspnoea. Pain simulating that in angina pectoris may occur, possibly by pressure of air upon the pulmonary and mediastinal vessels. The heart action may be interfered with by pressure from the distended lungs, by lack of blood arising from systemic and pulmonary venous congestion or by direct pressure of air bubbles in the praecordium and posterior mediastinum. When air escapes into the subcutaneous tissues, into the retroperitoneum, or even into the pleural cavities without producing a bilateral or tension pneumothorax, the condition tends to be benign, since the pressure in the mediastinum is relieved. When the air cannot escape from the mediastinum and the pressure rises too much, the condition becomes malignant and may then be fatal. Air in the mediastinum and interstitial tissues of the lung may be occult. It accompanies a wide variety of clinical conditions and respiratory diseases. Factors predisposing to leakage of air are apparently toxins of certain infective diseases, particularly influenza. When the presence of air is diagnosed it may be withdrawn and thus the patient's life may be saved.

Macklin, Madge T, and Macklin, C C (1944) *Medicine, Baltimore*, 23, 281

ENDOMETRITIS, CERVICITIS, AND METRITIS

See also B E M P, Vol IV, p 574

Cervicitis

Chronic cervicitis

Discussion of main complications—Strachan discusses the commoner non malignant pathological conditions of the cervix and their treatment. Dilatation (up to a No 12 dilator) of cervical stenosis, which is usually most marked at the internal os, will often relieve associated dysmenorrhoea in young nulliparae and occasionally sterility due to unsuspected intracervical catarrh. Cervical infection commonly supervenes upon lacerations sustained during parturition, with production of a hypertrophic erosion and leucorrhoea. Later, inflammation may extend to the parametrium, uterus and uterine tubes, giving rise to iliac pain, menorrhagia, tubal abortion or sterility. Chronic irritation, discharge and unstable epithelial conditions predispose to carcinoma. Direct treatment of the erosion should commence about 6 weeks after confinement, with application, after removal of sticky discharge, of an antiseptic such as 1 per cent mercurochrome twice weekly for 8 weeks. Electrocauterization of the erosion or amputation of the cervix is indicated for chronic cervicitis in younger and older women respectively. Sulphathiazole medication is usually effective for acute gonorrhoeal cervicitis, for chronic gonorrhoeal cervicitis, treatment is as outlined for an infected traumatic erosion, plus vaginal insufflation with powdered sulphonamide. Mucous polypi, usually associated with chronic cervicitis, if occurring in the middle-aged, require removal and exploratory curettage in order to exclude carcinoma. Fibroid polypi, originating at submucous fibromyoma from the body of the uterus, require removal by torsion of the pedicle and occasionally, if very large, by morcellation in fragments. sessile cervical fibroids, often causing sudden urinary retention, should be enucleated and the resulting cavity packed for 12-24 hours.

Strachan, G I (1945) *Med Pr.*, 213, 148

in Great Britain and who was harbouring a bacillus of unknown Vi phage type, cultures were sent to Pretoria University; here in 1944 identical phage types were isolated from 2 patients from the Johannesburg district and from one in Pretoria General Hospital. A symptomless carrier of paratyphoid B bacillus, who had disappeared during an outbreak, was rediscovered 2 years later amongst employees of a factory in which sewage effluent was being investigated for the typhoid bacillus. The author suggests that, in the case of recovered patients, continued observation based on Vi titres may lead to eradication of typhoid fever.

Felix, A. (1944) *Brit. med. Bull.*, 2, 269.

ENURESIS

See also B.E.M.P., Vol. V, p. 77; and Cumulative Supplement, Key No. 420.

Treatment

Aetiological basis of treatment

Backus and Mansell discuss the investigation and treatment of nocturnal enuresis among soldiers in 277 unselected consecutive cases. On admission all the patients received a general physical and psychological examination and 232 had a bladder function test. The average age was 21.33 years and the mean intelligence was slightly above the average. A percentage of 80.15 fell into the medical category A and 75.81 per cent complained of bed-wetting since infancy. The chief factors influencing the complaint were lack of early training, unhappy homes, operations and accidents, air raids, death of parents, and maladjustments to life in the Forces. Sexual disturbances affected only a small number; 43.32 per cent showed lack of training only without noticeable emotional upset. There was little relevant family history. No physical abnormality was shown by 92.06 per cent. Of the remainder, apart from 7 cases of genito-urinary disease, the complaints were apparently unconnected, such as bronchitis. Spina bifida occulta was seen in 13 out of 104 patients who were x-rayed. Cystometry showed that just under 25 per cent had small bladders, and the degree of voluntary control varied. Psychological examination showed that 48.01 per cent of the total number of subjects were of an immature type from unhappy homes, and sometimes had schizoid tendencies. No especial abnormal emotional history was noted in 27.07 per cent who appeared to be indifferent to their trouble. The remainder showed varying types of psychopathic personality. Treatment consisted in barring fluids after 6 p.m., explaining to the patient the physiology of the bladder and teaching him to practise positive control of bladder function by day and by night. Night control was fortified by autosuggestion at the time of going to sleep. Drugs were found to be of little value. In addition, general physical and operational therapy were given. It was found that success in treatment occurred chiefly in patients who had bladders of the normal size, were of reasonable intelligence and were under 30 years of age.

Inflammatory lesions in urinary tract

Winsbury-White describes inconspicuous and usually overlooked inflammatory lesions in the urinary tract which cause enuresis. In any case in which urine examination proves to be negative and bladder and genitals are apparently normal sufficient careful examination may reveal minor local lesions, especially in the urethra. Detailed study of early cases suggests that enuresis is often associated with inflammatory conditions in bladder or urethra. In long-standing cases bladder signs may be inconspicuous or absent yet expert investigation will reveal some inflammatory focus in the urethra, especially in cases in which enuresis has persisted from childhood into adult life. Chronic inflammatory changes in the urethra or at the bladder neck not only cause enuresis in children but are probably the original foci of infection in other urinary tract conditions. Cystoscopic examination of a large number of children aged between 4 and 5 years revealed with great regularity evidence of inflammation, sometimes only in patches. Because enuresis ceases on admission to hospital it must not be assumed that change of environment is the only treatment needed. Cystometry is not to be relied on for diagnosis; Campbell found that parasympathetic imbalance (hypertonic) and inflammation of the deep urethra produced similar curves. The author emphasizes the excellent results of skilful urethral dilatation in properly selected cases and advocates treatment at a centre at which experienced operators are available who will use dilatation neither too soon nor too often. Relapses are not uncommon and may be due to inflammatory conditions outside the urinary tract; the decision whether or not dilatation should be repeated may need very careful judgment. As long ago as 1888 Sir Henry Thompson treated enuresis by passing a catheter. After dilatation, enuresis ceased for periods varying from 3 months to 2 years in 58 per cent of 310 cases reported on by the author in 1941. Winsbury-White points out that in the absence of urethral pathology enuresis obviously will not respond to urethral dilatation. The criticism that urethral dilatation has been tried and failed ignores the importance of skilled technique. Enuresis starting in adolescence or later is often due to inflammatory lesions which respond well to treatment.

Backus, P. L., and Mansell, G. S. (1944) *Brit. med. J.*, 2, 462.

Winsbury-White, H. P. (1944) *Brit. J. Urol.*, 16, 81.

EPILEPSY

See also B.E.M.P., Vol. V, p. 96; and Cumulative Supplement, Key Nos. 42.

Aetiology

Lesions of the brain

Experimental epilepsy and the electroencephalograph.—Electroencephalic

and every effort was made to simulate the usual gastroscopic technique. The leading flexible rubber tip of a Cameron-Schindler standard gastroscope was injected with an emulsion of barium sulphate along its entire central longitudinal axis in order to assist in identifying its position. The gastroscope is sufficiently flexible to pass through the normal channels without any undue stress or strain. The greatest degree of flexion of the instrument occurs in the oesophagus and amounts to 10° . A lesser degree of flexion takes place in the fundus of the stomach just below the cardiac orifice. After the stomach has been inflated with air, the gastroscope can be passed down to its greatest depth for viewing the antrum and pylorus. Inflation causes no great discomfort or danger, unless the walls are weakened by serious organic disease. The air in the stomach casts an identifiable radiographic shadow. In the lower pole of the stomach the tip of the instrument is flexed acutely, but it conforms quite well to the contour of the greater curvature and the adjacent anterior wall. The shaft of the gastroscope lies almost in a straight line in close apposition to the posterior gastric wall. The blind areas of the stomach are due to the oblique angle of vision or to the short focusing distance. These areas consist of a narrow strip of the posterior gastric wall which is in close contact with the gastroscope, the lesser curvature of the antrum and a portion of the greater curvature of the fundus. Unless there is some modification of the present type of instrument it will be impossible entirely to eradicate the blind spots, and gastroscopic failures will occur from time to time.

Bannister, Freda B. and Macbeth R. G. (1944) *Lancet*, 2, 651

Brown, S. (1945) *Radiology*, 44, 143

Hufford, A. R., and Stonehouse, G. G. (1945) *Amer J digest Dis*, 12, 61

Tanner, N. C. (1944) *Brit med J*, 2, 849

ENOPHTHALMOS AND EXOPHTHALMOS

See also B E M P, Vol V, p 42

Exophthalmos

Causes

Thyrotrophic exophthalmos—Mulvany discusses thyrotrophic exophthalmos. This is not a common disease and is characterized by exophthalmos and hyperthyroidism, one of these may predominate or both may be fully developed. Some mild cases never progress beyond the first stage. The exophthalmos results from raised retrobulbar pressure, the consequence of pathological changes in the eye muscles which cause enlargement of their volume. Hyperthyroidism is not concerned in the mechanism. The development of the exophthalmos may be divided into three stages as follows: (1) A stage in which the proptosis develops owing to the swelling of the muscles, (2) a stage in which there is oedema and congestion and a rise of intra orbital pressure, which generally progresses to stage (3) corneal ulceration with consequent loss of the eye. The patient may complain of pain behind the eye or ophthalmic neuralgia and lacrimation and less commonly of photophobia, diplopia and difficulty in convergence. The proptosis is an early sign, it may be of unequal development and progression may be slow, but it may be rapid as in the acute exacerbations which may follow thyroidectomy. The differential points from thyrotoxic exophthalmos are the subjective phenomena, the not infrequent unequal development, the degree of proptosis, the sensation of hard resistance in an estimation of retrobulbar tension, the absence of lid spasm, the congestive features and the rarity of dislocation of the globes. Treatment lies in direct and indirect measures for the purpose of reducing the thyrotrophic and gonadotrophic output of the hypophysis. X-ray treatment as in acromegaly may be given with variable results. Iodine and oestrin may be given. Thyroid extract is more potent, and although it may appear paradoxical to give it to a patient with hyperthyroidism, it may lead to improvement in the unrelated exophthalmos. Of local operative measures when they are necessary in the second or progressive stage, Naffziger's orbital decompression or some modification of it offers the best chance of helping the patient. Mulvany stresses the need for accurate diagnosis of cases of exophthalmos.

Mulvany, J. H. (1944) *Amer J Ophthal*, 27, 693

ENTERIC FEVERS

See also B E M P, Vol V, p 50 and Cumulative Supplement, Key Nos 417-419

Typhoid fever

Carriers

The Vi bacteriophage—Felix describes the typing of typhoid and paratyphoid B bacilli with Vi bacteriophage and Vi agglutination tests to aid detection of typhoid and paratyphoid B carriers. Craigie and Yen discovered in 1938 that strains of typhoid bacillus can be divided into well defined types according to their sensitivity to type-specific anti-Vi bacteriophages, the application of this principle to paratyphoid B as well as to typhoid bacilli aids greatly in the detection of carriers. The phage type of a strain being for all practical purposes, a permanent character, connexion can be proved or disproved between typhoid fever cases occurring sporadically or during an epidemic and between a carrier and the patient for whose infection he is held to be responsible. Bradley described the tracing to a persistent carrier on a farm a hundred miles away, of 23 apparently sporadic cases of typhoid fever which occurred over a period of 2 years in 4 counties and 10 administrative districts. In the case of a carrier who was infected in South Africa more than 40 years before he was responsible for an outbreak

in Great Britain and who was harbouring a bacillus of unknown Vi phage type, cultures were sent to Pretoria University; here in 1944 identical phage types were isolated from 2 patients from the Johannesburg district and from one in Pretoria General Hospital. A symptomless carrier of paratyphoid B bacillus, who had disappeared during an outbreak, was rediscovered 2 years later amongst employees of a factory in which sewage effluent was being investigated for the typhoid bacillus. The author suggests that, in the case of recovered patients, continued observation based on Vi titres may lead to eradication of typhoid fever.

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Inflammatory lesions in urinary tract

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Winsbury-White, H. P. (1944) *Brit. J. Urol.*, 16, 81.

EPILEPSY

See also B.E.M.P., Vol. V, p. 96; and Cumulative Supplement, Key Nos. 424-432.

Aetiology

Lesions of the brain

Experimental epilepsy and the electroencephalograph.—Electroencephalographic observa-

tions were made by Pacella, Kopeloff, Barrera and Kopeloff on 5 monkeys, each weighing 3-4 kilograms, to one side of the cerebral motor cortex of which were applied small round laminated linen discs containing, in a depression, aluminium hydroxide cream. Ten monkeys were used as controls, to the cortex of which either empty discs or discs containing innocuous substances were applied, and as further controls, 3 monkeys which had not undergone any operative measures were used. After a latent period of from 3 to 8 weeks, the aluminium hydroxide caused chronic Jacksonian and generalized seizures for periods extending over 2 years after operation. None of the control animals had seizures of any kind. Abnormal electroencephalographic activity was indicated by frequent delta waves and marked irregularities in the pattern, and this occurred in all 5 experimental monkeys. There was usually no difficulty in determining unilateral abnormality, and in general there was fairly close correlation between this and localization of symptoms. The electroencephalograms of the operation control animals showed delta activity, usually consisting of 4-6 cycles per second, round the operation site for 2 or 3 weeks afterwards. (The incidence of these potentials disappeared in the course of the subsequent few weeks.) The 3 monkeys which had not been operated on showed no such abnormalities. From previous histopathological studies of similar material, the presence of foci for the discharge of abnormal potentials in the region of the applied discs appeared to indicate a physiological zone of hyperexcitability, and not to be the result of specific tissue damage.

Pacella, B. L., Kopeloff, N., Barrera, S. E., and Kopeloff, L. M. (1944) *Arch Neurol Psychiat*, Chicago, 52, 189

EPIPHYES, DISEASES AND INJURIES

See also B E M P, Vol V, p 127

Injuries: separation or displacement

Separation of upper epiphysis of femur

Treatment by traction and hip spica—Green discusses the diagnosis and treatment of slipping of the upper femoral epiphysis. Both hips were affected in 10 of 26 patients. Trauma was an aetiological factor in 5 patients and there were several other instances of injury precipitating the acute symptoms. The condition usually occurs in obese adolescents. The symptoms are often intermittent and consist of limping, with pain in the hip, thigh or knee. Physical examination discloses limitation of internal rotation, flexion and abduction of the hip, with pain and spasm in the extremes of these movements. The earliest radiological findings are rarefaction of the neck of the femur in the region adjacent to the epiphyseal line, and anterior displacement of the neck of the femur in the region adjacent to the epiphyseal line, and anterior displacement of the neck of the femur in the region adjacent to the epiphyseal line, and anterior displacement of the neck of the femur in the region adjacent to the epiphyseal line. The author employed the traction-spica-traction method in the treatment of 18 hips in which the displacement ranged from minimal to moderate. In this method two traction forces are applied to the involved extremity for an average period of 3 weeks, one longitudinally and the other to develop internal rotation. A hip spica is applied as soon as the relief of spasm is accompanied by the maximal degree of abduction and internal rotation. The spica is removed 3 months later, and restoration of function is accomplished by counterpoised traction and active movements. All patients treated by this method were found to have a normal coefficient of motion 6 years after treatment. The results were nearly as good in 5 cases treated by nailing *in situ*, but closed manipulation was considered to be an unsatisfactory procedure. In 3 of 4 cases of severe displacement open reduction with skeletal fixation resulted in good function. The outcome was poor in the fourth case owing to the development of aseptic necrosis. This complication is less likely to occur if the retinacular vessels are preserved.

Green, W. T. (1945) *Arch Surg*, Chicago, 50, 19

ERYTHEMA

See also B E M P, Vol V, p 159, and Cumulative Supplement, Key No 442

Erythema due to internal causes

Conditions allied to erythema multiforme

Erythema elevatum diutinum—Ketrion describes a case of erythema elevatum diutinum occurring in a middle-aged woman. The lesions were first seen on the feet and ankles and consisted of purple smooth papules of various sizes. The patient was under observation for 9 years, during which period the eruption was observed on the arms, buttocks and knees. The colour of the patches ranged from a dark grey to a deep red or purple, and the configurations were irregular, especially on the arms. In some instances the lesions disappeared, leaving a slight pigmentation. Other lesions assumed the appearance of keloidal formation. The fibrous changes appeared much earlier on the arms than they did on the lower extremities. Specimens removed for biopsy showed perivascular collections of polymorphonuclear leucocytes and a material termed toxic hyalin. The walls of the blood vessels were disrupted and cells and lymphocytes. Crocker considered that the lesions of erythema elevatum diutinum were analogous to subcutaneous rheumatic nodules. A rheumatic background is not present in all cases, however. The disease is of unknown aetiology and is entirely different from granuloma annulare. The condition does not respond to any form of treatment.

Clinical picture

Erythema due to internal causes

Erythema nodosum—Among records of 536,380 patients discharged during 14 years from

a New York hospital, Lincoln, Alterman and Bakst found only 42 cases of erythema nodosum; the authors quote reports from two other large United States hospital services which also indicate its infrequency. Hence its use in differential diagnosis is much less in America than it is in northern Europe where the reported incidence of erythema nodosum is great. Of 14 patients aged between 13 and 26 years, of whom 64 per cent were female, 3 had rheumatic fever and only one had active tuberculosis. Of 28 patients aged between 2 and 12 years, 15 being boys, 27 had tuberculin tests to which 20 reacted positively. The percentage of positive reactors among these children with erythema nodosum was 3 or 4 times the incidence noted among the child ward population of the hospital. Among 362 children over 2 years of age with active primary tuberculosis, erythema nodosum was observed 13 times—including 11 cases among the 20 positive reactors already cited—9 times as a symptom complex associated with onset of the primary focus and 4 times later in the course of the primary disease. Among 325 cases of calcified primary pulmonary tuberculosis there were only 3 cases of erythema nodosum, in 2 of which acute rheumatic fever was concomitant. Lincoln, Alterman and Bakst conclude that every child with erythema nodosum, being potentially tuberculous, needs complete investigation for the purpose of establishing the diagnosis. Since the aetiology of erythema nodosum apparently varies in different age groups, the contradictory literature concerning its aetiology may be due to reports on groups of patients of varying ages.

After discussing the literature of erythema nodosum in detail, Perry reports on the investigation of a series of 112 cases, 74 females and 38 males. A Mantoux test was done in all cases, a few patients were tested with streptococcal nucleoprotein, and all patients were examined by x-rays and subsequent contact was maintained with them. Sixty-one gave a strongly positive Mantoux reaction and 51 were negative. Perry considers that in view of radiological and other supporting evidence 32 cases were clearly tuberculous and 28 with positive Mantoux tests but without other evidence were probably tuberculous. Thus in the whole series 28 per cent were certainly, 25 per cent were probably, and 45 per cent were distinctly not, tuberculous. Dividing the series into two groups above and below the age of 15 years, the author found that there were 36 boys and 31 girls in the lower age group of whom 43 per cent certainly and 29 per cent probably were tuberculous. This great incidence of cases of tuberculous aetiology in children of school age is, Perry states, of obvious importance in the diagnosis of tuberculosis. In only 10 of all cases had the patients had acute rheumatism and in only 2 was there any evidence of relapse; in both of these the rheumatism appeared to occur after the erythema nodosum rather than to be coincident, a position which supports the theory that although the two diseases both may result from a streptococcal infection they are not necessarily the same. The author concludes that the results of the analysis of this series agree with those of other workers that erythema nodosum should be regarded as a result of a non-specific reaction to a variety of infections or toxic agents in constitutionally disposed people; this is suggested by the fact that in only a proportion of cases does erythema nodosum develop in any type of infection.

Relationship of erythema multiforme and herpes simplex.—The probable aetiological relationship between erythema multiforme and herpes simplex and the treatment of the erythema is discussed by Anderson. Erythema multiforme has been described as occurring after smallpox vaccination and during the course of many and various infections. The association with menstruation has been noted. The tendency of the disease to recur in the spring and the autumn suggests that atmospheric conditions may play a part. Forman and Whitwell noted the frequent association of erythema multiforme with herpes simplex and tabulated the clinical similarities of the two diseases. During the last 10 years repeated vaccinations with smallpox vaccines have been used successfully in about 80 per cent of cases for the purpose of preventing recurrences of herpes simplex. The method used is that of a scarifying vaccination with smallpox vaccine which is repeated at fortnightly intervals on 4 or 5 occasions. The author has used this procedure during the last few years as preventive therapy for recurring erythema multiforme associated with herpes simplex and also in cases in which no such association was established; in several cases the treatment has been of distinct value. Anderson states that in the absence of experimental confirmation the relationship between the two diseases must be a matter of speculation, but in our present state of knowledge it can be said that in many instances herpes simplex has some relationship to erythema multiforme.

Anderson, N. P. (1945) *Arch. Derm. Syph., N.Y.*, 51, 10.

Ketron, L. W. (1944) *Arch. Derm. Syph., N.Y.*, 50, 363.

Lincoln, Edith M., Alterman, Janet, and Bakst, H. (1944) *J. Pediat.*, 25, 311.

Perry, C. B. (1944) *Brit. med. J.*, 2, 843.

EYE EXAMINATION

See also B.E.M.P., Vol. V, p. 216.

Instruments and technique of using them

The ophthalmoscope

Its uses in diagnosis generally.—Bedell, discussing ophthalmoscopy in the diagnosis of disease, points out that owing to the similarity between the fundus vessels and those of other parts of the body, information about their state, which is not otherwise obtainable, may be gathered from an examination of the eye. Central retinal artery blockage may be diagnosed

and the author believes that spasm is the cause in cases in which recovery takes place, but he holds that when blockage is due to an embolus search for an aetiological cause must be instituted. Venous occlusion, unlike arterial blockage, results in an eye full of blood, the veins are engorged, with much or little bleeding in, on or above the retina. Central retinal vein thrombosis may end in resolution, organization of scar tissue, or glaucoma. In regard to arteriosclerosis the author emphasizes that vein compression by a stiff artery may occur in physiologically normal arteries and is of significance only when it is accompanied by other signs. Each case of arteriosclerosis must be considered as a whole. In Bedell's experience, fundus reports cannot be correlated with the need for operation in hypertension. Attention should be devoted to the fundus in investigating possibilities of earlier diagnosis of hypertension. In a patient with a previously known comparatively normal fundus, the occurrence of fresh to localized oedema or haemorrhages is indicative of a breakdown and if dark brown or granular haemorrhages occur deep in the retina the prognosis will be grave. The retinitis of pregnancy is similar to that of acute nephritis, its preceding signs are often overlooked and spasm of one or more retinal arteries may be the first ophthalmological danger sign. The presence of small hard yellow exudates and scattered haemorrhages with or without vessel changes calls for the exclusion of hyperglycaemia. Bedell briefly discusses papilloedema and states that the condition should always be excluded in patients complaining of headache. Senile macular degeneration must be recognized as a cause of failing vision in the elderly.

Dark-adaptation tests

Essentials for accuracy—Goddling, in describing an instrument for testing dark adaptation, emphasizes the necessity of adopting standard conditions in whatever method is used. Standard pretreatment of the subject is ensured by incorporation of a light-adapting apparatus the brightness of which, viewed for 5 minutes, gives a standard 'bleaching' exposure. The test light unit contains one neutral density filter transmission $\frac{1}{10}$ and two filters transmission $\frac{1}{100}$ which can reduce the brightness of the test field or object by $\frac{1}{10}$, $\frac{1}{100}$ and so on as well as one fixed and one rotatable polaroid disc, by which intermediate stages of brightness can be achieved. A lamp of constant brightness illuminates a sand blasted pot opal glass screen, the reflecting surface of which is viewed by the subject at a distance through polaroids and filters as required. The scale attached to the rotating polaroid is graduated so that by varying the positions of polaroids and filters, the brightness can be decreased in steps of 0.05 logarithm unit from a maximum of 400,000,000 micro micro lamberts to a minimum of 400 micro micro lamberts. The test is carried out at a distance of 2 feet, at which distance the diameter of the test object—an arrow, rotatable to point in any one of 4 directions—subtends a visual angle of 7° , the arrow's size as a conditioning factor is eliminated since the shape has been so designed that no part is seen as such before the shape is appreciated as a whole. A binocular test is recommended. Vision under 6/18 requires previous correction. Data obtained by noting the times at which the subject sees successively lower brightnesses are plotted to give a dark adaptation curve, the final threshold reading usually being at flashes. In 9 of 12 subjects given duplicate tests at short intervals, the results were almost identical. This Goddington suggests, constituted satisfactory evidence of the reproducibility of the test considering that some variation due to biological causes was probably included.

Bedell A J (1945) *Amer J Ophthal*, 28, 139

Goddington, E W (1945) *Proc R Soc Med*, 38, 155

FALLOPIAN TUBES DISEASES

See also B E M P, Vol V, p 250

Tubal pregnancy

Aetiology

Review of over two thousand cases—With the object of assessing avoidable factors and fixing responsibility, Williams and Corbit analyse the histories of 101 deaths which occurred among 2,204 patients with ectopic gestation. Factors considered included age, race, parity, present history, time of seeking medical aid after onset of symptoms, diagnosis interval from operation and time of death after operation. In 36 cases diagnosis was made only at necropsy to haemorrhage in 19 to infection and in 10 to medical complications. In 68 cases death was due as non preventable the patient died either despite prompt correct diagnosis and adequate surgery with transfusions, or because medical complications had occurred. In 18 cases the patient was held to be responsible because of attempts at criminal abortion, usually combined with misleading history, refusal to go into hospital or delay in seeking medical aid. Lack of education of the general public regarding early adequate antenatal care and the gravity of pain and vaginal bleeding in association with amenorrhoea could be remedied. In 13 deaths the diagnosis had been correct, for delay in sending the patient to hospital owing to non-recognition of the acute emergency nature of the case. The hospital chief was held to be solely responsible in 45 deaths, and in 7 cases was jointly responsible with the referring physician. The avoidable factor was considered to be error in judgment, with such underlying factors as failure in diagnosis, unexplained delay in or lack of operation, the performance

of multiple non-essential operations—for example appendectomy—in the presence of an acute condition dangerous to life, poor choice of operative procedure and failure to treat shock adequately. Only 37 women received blood transfusion, of whom only 4 had more than one transfusion, although in the majority of cases the time interval would have allowed more than one to have been given.

Williams, P. F., and Corbit, J. D. (1944) *Amer. J. Obstet. Gynec.*, 48, 841.

FIBROSITIS

See also B.E.M.P., Vol. V, p. 279; and Cumulative Supplement, Key No. 489.

Clinical picture

Panniculitis

Notes on a fatal case.—Friedman describes a fatal instance of panniculitis in a 23-year-old white woman, although he says "the present case is not entirely typical of Weber-Christian disease as originally described", and "the patient obviously died of staphylococcal septico-pyemia and not of panniculitis as such". There was a long history of painful nodules on the legs and in one breast, accompanied by pyrexia. The patient was admitted to hospital with a temperature of 105.8° F. and a leucocyte count of 1,000 per cubic millimetre. There was an ulcerated lesion measuring 10 × 15 centimetres on one thigh with induration extending over the inguinal region. Food was not tolerated and transfusions and intravenous fluids were administered. Systolic murmurs, gallop rhythm and cardiac enlargement developed and the patient died, disorientated and comatose and with a terminal temperature of 106.7° F., one month after admission. Biopsy showed granulomatous inflammation involving predominantly the subcutaneous fat lobules, round cells and large mononuclear cells being most abundant. The conditions observed in the viscera at necropsy did not throw light on the essential nature of the disease, and the changes in visceral adipose tissue described by Spain and Foley were not observed. Microscopical examination after necropsy showed that the lobules of adipose tissue beneath the intact epidermis were infiltrated by inflammatory cells as was the fat surrounding the dermal appendages. The cells, chiefly large mononuclears and macrophages, were concentrated around the margins of the lobules and the intervening fibrous septa were less heavily infiltrated than was the fat, a feature distinguishing the condition from erythema nodosum and erythema induratum.

Friedman, N. B. (1945) *Arch. Path.*, 39, 42.

FILARIASIS

See also B.E.M.P., Vol. V, p. 301; and Cumulative Supplement, Key Nos. 490–495.

Filariinae

Wuchereria bancrofti

Use of lithium antimony-thiomalate.—Brown discusses the treatment of filaria infection with lithium antimony-thiomalate. A 6 per cent solution is used, 1 cubic centimetre containing 60 milligrams of lithium antimony-thiomalate. A series of 12 patients was treated; they were medically examined beforehand and blood counts and urine examinations were made before, after and during treatment. Injections of 3 cubic centimetres into the gluteal muscles were given to adults at regular 24-hour intervals. The first dose was half-size in order to ascertain sensitivity. Results were measured by microfilaria counts on 0.1 cubic centimetre of blood drawn between 10 and 10.30 p.m. Even on disappearance of microfilaria from the blood, it is necessary to continue examination of the blood for several months after cessation of treatment to ascertain whether the adult worms also were killed. In this series the microfilaria count was reduced by 85–100 per cent, this reduction being maintained 4–5 months after completion of treatment. One patient failed to respond to the treatment. The maximum reduction occurred after 15–20 cubic centimetres of the drug had been given; after this the rate was slower. Physical examination of the patients 4–5 months after treatment showed no pathological changes due to death of the adult worms of the microfilariae and did not show any reduction in size of enlarged lymphatic glands. Toxic effects of the drug include vomiting, starting after repeated injections, joint pains, slight fever and rash, but these are not considered sufficient to preclude further trial with this drug. There is no other therapeutic agent available that may be curative.

Surgical treatment of elephantiasis.—Bankoff, dealing with the surgical treatment of elephantiasis, recognizes a primary or filariasis type and a secondary type due to persistent chronic lymphatic obstruction. He outlines the aetiology, the commonest infecting agent being the *Filaria (Wuchereria) bancrofti*: the worms enter the lymphatic system, mature there and block the lymph channels. *Culex fatigans* is the mosquito which transmits the infection. The best surgical results are obtained in scrotal elephantiasis: the testes usually are sacrificed and the scrotum is cut down to normal size while the patient is under the influence of morphine and scopolamine (hyoscine) injections and local block anaesthesia. Sepsis can be eliminated by packing the wound with sulphonamide powder. For the limbs, 3 operative procedures are briefly described. (1) Kondoleon's method. Two or more strips of skin, subcutaneous tissue and sufficient muscular fascia are excised from each side of the thigh and leg permitting drainage from the superficial blocked lymphatic into the deep lymphatic vessels. (2) Auchincloss's method. The first stage is the control of existing inflammation by means of physiological saline applied to vertical incisions at the limits of the infected areas. In the second

stage various incisions—inguinal lower third of thigh, upper third of leg and ankle—are made on the anterior and posterior surfaces of the limb. For the purpose of creating a new lymphatic system silk threads on long flexible needles are introduced, the wounds are closed and a sulphonamide powder dressing is applied. (3) Homan's method aims at a plastic result by repeated excisions of skin, subcutaneous tissue and muscular fascia at 4 weekly intervals and at one part of the limb at a time. The author prefers Kondoleon's method.

Bankoff, G (1944) *J trop med (Hyg)*, 47, 49

Brown, H W (1944) *J Amer med Ass*, 125, 952

FOETUS DISEASES, MALFORMATIONS AND MONSTROSITIES

See also B E M P, Vol V, p 334, and Cumulative Supplement, Key Nos 503-512

Fetal diseases

Tuberculosis

Clinical importance of congenital tuberculosis—Loewenstein doubts whether death from miliary tuberculosis is inevitable within 6 months in cases in which infants are congenitally infected with tuberculosis. He quotes 2 necropsy reports suggesting healed congenital infections. Zarel reported on one with healing foci in the liver, Chiari described another showing a large completely healed focus in the liver and a probably primary focus in one lung in a child who survived for 30 months and then succumbed to a meningitis described as 'accidental'. The author discusses the mechanism of uterine infection. He has not found in the literature any convincing evidence of germinal infection in human beings, transmission must therefore, he argues, be haematogenous. Calmette and Shenk reported, in 1933 the presence of virulent tubercle bacilli in the umbilical cords of 5 babies of tubercular mothers. Loewenstein co-operating with Viennese obstetricians, obtained blood samples from 56 tuberculous mothers and the respective umbilical cords, 8 cultures from mother and child were positive. In course of examination of blood from 200 apparently healthy mothers and umbilical cords both blood samples were positive in only 2 cases and the babies were apparently healthy and tuberculin negative during a year's observation. Reports by various investigators prove that placental tuberculosis is commoner than is generally supposed. Siegel's analysis of necropsy reports suggests that direct tuberculous invasion of the infants' lungs occurs from establishment of a placental tuberculous focus about 4 months before delivery, the bacilli are either killed or arrested, probably the latter, in the liver but the intensity of the invasion may overcome this barrier.

Abnormal conditions occurring in living fetus

Respiratory system

Congenital aplasia of the lung—Garber reports on a case of congenital aplasia of the lung in a child who had been observed for 7 years. The patient was somewhat underdeveloped, weighing 31 pounds (average 38 pounds). There was a past history of colds and coughs, and when he came under observation he had had a tuberculous contact with his aunt. On examination there was marked contraction of the left hemithorax, a flat percussion note and diminished breath sounds except at the apex. Radiologically the left hemithorax was opaque with the heart near the left lateral chest wall. Two x ray examinations during the next 5 years showed no change. The patient was in good health until he had an attack of bronchopneumonia in 1941. Bronchograms under bronchoscopic control showed the left main bronchus to be about 1.5 cubic centimetres in length and two bronchi to be 2 millimetres in diameter, it was concluded that there was a congenital failure in the development of the left bronchial tree and lung. Discussing the condition, Garber states that the congenital abnormality is asymptomatic. Slight flattening and diminished movement may be found on the affected side, the heart and mediastinal structures are displaced towards the side on which the lung is absent. The occurrence is more commonly seen on the left side. It is compatible with a normal span of life, if the first year of life is survived. Displacement of the heart and mediastinum, elevation of the ipsilateral diaphragm and narrowing of the intercostal spaces on the affected side are seen in x ray pictures. Bronchoscopy and bronchography are the most important procedures in establishing the differential diagnosis from paralysis of the diaphragm, congenital absence of the diaphragm, diaphragmatic hernia and bronchial foreign bodies.

Genito-urinary system

Artificial vagina—When the lower ends of the two Müllerian ducts fail to develop, absence of the vagina ensues, there being seen only the vestiges of a vagina in the form of a depression in the perineum from the development of the external genitalia. For the purpose of remedying this defect, Brady describes four methods of constructing a vagina, an operative procedure, which has not been previously described, was used in one of his own cases. A normal adult metre covered with mucous membrane. A circular incision was made around the outer margin of the mucous membrane and by blunt dissection the tissues were stretched until a tunnel, 7 centimetres deep and capable of admitting 2 fingers, was formed. The small circular piece of mucous membrane which had originally covered the immature vagina was pushed upwards until it rested upon and covered the top of the newly made vagina. In order to cover the raw surface the labia minora were dissected off, the mucous membrane was split from large folds to flat surfaces and, in the form of flaps with pedicles, sewn deeply into the vagina. An artificial phallus was inserted for the purpose of keeping the vagina dilated. The second

patient had not even a dimple in the perineum and operation was refused. By direct pressure with a Pyrex tube, applied midway between urethra and anus, a depression was made and by frequent application was gradually deepened until after 6 months it was 6 centimetres in depth and could admit 3 fingers. This patient married and had satisfactory sexual relations. The third patient had a depression 1 centimetre deep and a pelvic mass that was considered to be an enlarged uterus. At operation a cavity 7 centimetres long was constructed; the abdomen was opened and the mass was found to be the patient's only kidney. The abdomen was closed and a phallus of balsa wood was inserted into the newly formed vagina. The fourth patient had a small depression just below the urethra. An inverted U-shaped incision was made just below the urethra, extending backwards to the anus. The tissue was undercut from above downwards, leaving a pedicle anterior to the anus. By blunt dissection a cavity was constructed capable of admitting 2 fingers to a depth of 8 centimetres. The anal flap was sutured deep in the cavity so as to form its posterior wall.

Congenital absence of uterus and vagina.—Cyclic ovarian changes occurred in the mucosa of an artificial vagina produced by Ayre, without resort to major surgery, in a girl with congenital absence of uterus and vagina. The artificial membrane was induced to grow up from her vulval mucous membrane by the following technique. The initially produced one-finger opening between bladder and rectum was kept open by insertion of a wax mould which was worn for 6 weeks, but was removed weekly to allow of cleansing of the cavity. Gradual upgrowth of the squamous epithelial zone proceeded. The passage was then dilated and deepened and a larger obturator inserted. The procedure was repeated at intervals of 1–2 months; 4 successive sizes of obturator were used until one measuring $5 \times 1\frac{1}{2}$ inches was accommodated. After completion of squamous epithelization, vaginal smear studies taken daily over a period of 2 months showed that the morphology of the squamous epithelial cells varied as it does in the follicular and luteal phases of a normal vaginal mucosa. Of 100 epithelial cells counted, the number of cornified cells gives the cornification percentage. Daily cornification counts charted over the same period gave a cornification curve, representing variations in oestrin level. The curve showed a cyclic rise and fall, being highest during the follicular phase. From these findings the approximate times of ovulation and menstruation were postulated. Ayre concludes that cyclic phenomena in response to ovarian secretions occur in vulval squamous epithelium.

Ayre, J. E. (1944) *Amer. J. Obstet. Gynec.*, 48, 690.

Brady, L. (1945) *Ann. Surg.*, 121, 518.

Garber, R. L. (1945) *Amer. J. Roentgenol.*, 53, 129.

Loewenstein, E. (1945) *Amer. Rev. Tuberc.*, 51, 225.

FOOD

See also B.E.M.P., Vol. V, p. 388; and Cumulative Supplement, Key Nos. 513–518.

Vitamins

Vitamins A and D

Minimum requirements in various conditions.—Buckstein describes the part played by vitamins A and D in nutrition. He emphasizes the great importance of administration of vitamin D to the childbearing woman during the entire period of pregnancy, quoting Wolfe's observation that although infantile skeletal defects can be favourably influenced by later administration of vitamin D, changes in the teeth cannot be so influenced. Vitamin D when it is administered to the infant encourages the rate of growth and as well maintains the integrity of the skeleton. After surveying available evidence the author concludes that 300–400 units of vitamin D are sufficient for normal growth of skeleton and teeth and that the maximum influence on growth is obtainable with amounts varying between 300 and 600 units a day. The administration of vitamin D even to breast-fed babies is advocated and it is mentioned that premature infants may require twice as much vitamin D as do full-term children. On the toxicity of vitamin D, Buckstein quotes Warkany, Guest and Grabill who administered 400,000–500,000 units a day, after which the concentration of the vitamin in the serum rose to between 9,000 and 13,000 international units per 100 cubic centimetres, an amount equal to the antirachitic potency of cod liver oil. For tetany the author advocates in addition to vitamin D, administration of large doses of calcium—preferably in the form of calcium chloride—for the first week or 10 days of treatment, after which vitamin D alone may be administered. Buckstein states that osteomalacia and osteoporosis may be justifiably regarded as a form of adult rickets.

Vitamin C

Oranges and nutrition.—The South African Department of Public Health summarizes the more important nutritional facts about the orange, which is 75 per cent edible. The juice is as rich in vitamin C as is the pulp and the peel is fully twice as rich as either. The individual weight ranges from $4\frac{1}{2}$ to 9 ounces, with a corresponding range of vitamin C content from 50 to 105 milligrams. One medium-sized orange taken daily, providing 75 milligrams of vitamin C, will meet the daily requirement of 50 milligrams for a normal person of any age. As well as $\frac{3}{8}$ ounce of natural sugar, one medium-sized orange contains 0.6 gramme of calcium and 145 international units of vitamin A, i.e. 6 per cent and 5 per cent of the recommended standards of 1 gramme and 3,000 international units, respectively, for children up to 12 years of age. It contains predominantly alkaline mineral salts, the effect of which after absorption

in children is usually overcome by manipulation, or, in order to relax the spasm, Novocain (procaine hydrochloride) may be injected into the external popliteal nerve, and then a walking-plaster should be applied with the foot in the corrected position. The plaster may remain in place for 6–12 weeks.

Ingrowing toenail.—The various forms of treatment of ingrowing toenail are discussed by Wilson. Since a nail grows only from its root the relative ingrowing into the paronychium is due to an overgrowth of this tissue, and pressure on the nail results in necrosis and infection of the paronychium. The object of conservative treatment is to relieve pressure on the edge of the nail and so to allow the paronychium to recover. The treatment is most likely to be successful if the nail is allowed to grow and curve over the edge of the toe. The indication for radical treatment is the failure of conservative measures. Many operative measures have been advised; there is a high recurrence rate after simple avulsion of the nail and removal of the granulation tissue. Wedge resection of the nail, nail bed and soft tissues may be carried out and may be successful if the soft tissues are replaced at a level lower than that of the nail. Another method advised is partial amputation of the terminal phalanx with the nail; this procedure leaves an ugly toe, often with a tender end. Wilson states that in his experience the most satisfactory operation is removal of the nail, matrix of the nail root and hypertrophied paronychia. Prior to operation infection is reduced as much as is possible. Either an intravenous anaesthetic or local nerve block anaesthesia is satisfactory. A tourniquet facilitates the operation, but unnecessary pressure must be avoided. On both sides of the nail an incision is made and is prolonged proximally towards the side of the toe, ending before the line of the interphalangeal joint. The granulation tissue is removed, the nail is loosened and avulsed, the eponychium is dissected back until the capsule of the interphalangeal joint is disclosed and the nail bed is dissected off the phalanx. Any remnants of the matrix are removed with a sharp curette. After a dusting of sulphanilamide powder the flaps are replaced without suture and are kept in place by a firm Vaseline dressing which is left undisturbed for 10 days. The wound is then dressed with a 1 in 1,000 proflavine solution. The wound is usually healed and dry by the end of 3 weeks. The exposed nail bed in a few weeks becomes hard and dry and is not tender.

The arches of the feet.—Crisp maintains that a normal foot if properly used will seldom give trouble, but points out that even when all obvious deformities are excluded the majority of feet, although they may appear to be normal, have some minor fault which is a source of weakness and therefore of potential trouble. Slight abnormalities in the structure or functioning of the arches of the foot or in the muscles which support those arches or which move or stabilize the foot, will cause foot strain. Incorrect stance, posture or mechanism of walking will produce the same condition. The foot must be freely mobile if it is to fulfil properly its function of weight-bearing and propulsion, and even its size and shape are important considerations. Any deviation from the normal in any of these details is liable to cause the fatigue which is nearly always the cause of breakdown. Experience during the recent war, when men were unable to choose a job to suit their feet, disproved the widely held belief that foot trouble is almost exclusively a female complaint. Rest is the first and most essential principle in the treatment of foot strain, and sufficient time should elapse before taking any active steps to correct errors of stance or posture or before commencing faradic foot baths or any appropriate exercises to correct the improper functioning of the foot. If satisfactory shoes are worn, the only conditions which require arch supports are the high longitudinal arch and the dropped transverse arch.

Allan, F. G. (1944) *Med. Pr.*, 212, 248.

Crisp, E. J. (1944) *Brit. J. phys. Med. N.S.*, 7, 103.

Wilson, T. E. (1944) *Med. J. Aust.*, 2, 33.

FROST-BITE AND TRENCH-FOOT

See also B.E.M.P., Vol. V, p. 440; and Cumulative Supplement, Key No. 528.

Morbid anatomy

The blood vessels

Fluorescein tests.—Lange and Boyd describe the pathology of frostbite and the prevention of gangrene. Fluorescein tests suggest that the immediate reaction to cold is a decrease of the capillary permeability and parallel arteriolar contraction to decrease filtration pressure; the reaction is unaffected by local anaesthesia or sympathetic block or by large doses of nitroglycerin or amyl nitrite and appears to be due to axon reflexes. The freezing solid of exposed tissues leads to temporary complete interruption of circulation succeeded by a period, lasting from 6 to 16 hours after freezing, during which the fluorescein test demonstrates complete restoration of circulation and increased capillary permeability and this provides the optimum time for treatment, for it in turn is replaced by arteriolar and capillary occlusion due to erythrocyte clots and consequent gangrene. Observation of 14 frostbitten patients demonstrated that if the fluorescein test is applied 14 or more hours after an individual's exposure to frostbite, it indicates the amount of superficial tissue damage which may be expected. In 2 patients Novocain (procaine hydrochloride) block of the sympathetic ganglia failed to modify the fluorescein pattern, which proved that no essential part of the circulatory block was due to spasm. Although the fluorescein test affords useful information about the state of the deeper vessels in occlusive vascular disease, it may, in the case of frostbite, indicate

extensive surface structure loss when there is slight damage to deeper structures, of the 14 patients observed, for instance, only one needed debridement of 2 toes. The authors consider that the need for surgical conservatism in the treatment of frostbite can hardly be over-emphasized since the deeper tissues regenerate well after frostbite. The surgery employed for the treatment of occlusive vascular disease is therefore inapplicable. In 16 rabbits the administration of heparin during the circulatory restoration period prevented the gangrene which appeared in all the controls. All the animals, except one of those to which heparin had been given, suffered initial motor and sensory paralysis of the exposed area.

Pathological picture of lesions due to cold

Blackwood in an article on the pathology of tissue injury from exposure to low temperature, considers the effect of exposure to varying degrees of cold, from 18 to 15° C at which reversible damage may be done to skin and superficial tissues, to a temperature of between 5 and 10° C which causes freezing and death. Immersion in sea water or exposure to moist conditions for 22 hours or longer, at temperatures from 10 to -19° C causes blistering or gangrene of the skin. Damage to nerves, muscles and blood vessels is less obvious, but prolonged disability may result. Nerves show more or less extensive demyelination according to the severity and extent of the exposure. Regeneration is slow and if incomplete may cause severe pain. In the muscles of experimental animals partial hyaline necrosis, followed by partial regeneration and also by secondary degenerative changes due to denervation have been seen. Spasm of blood vessels occurs during exposure and dilatation when the patient is warmed. Thrombosis is found in veins near areas of necrosis or chronic infection. Cold sensitivity, the result of disturbance of the neurovascular mechanism, may occur, and osteoporosis is often found in bones, with ensuing recalcification. Cold sensitivity and osteoporosis also occurs in frostbite, a condition caused by temperatures below about -5° C in which there is rapid chilling of superficial tissues, crystallization of tissue fluids, rupture of cell walls and tissue death from direct effect of cold. Blood stasis occurs in the vessels at first, with thrombosis later, an inflammation which occurs with sloughing of dead skin and deeper tissues. Obliterative endarteritis is said to occur proximally to necrotic areas.

Blackwood, W (1944) *Brit med Bull*, 2, 138

Lange, K, and Boyd, L J (1945) *Surg Gynec Obstet*, 80, 346

FUNGIOUS DISEASES

See also B E M P, Vol V, p 448, and Cumulative Supplement, Key Nos 529-544

Ringworm infections

Ringworm of the feet and hands

A report on the effects of two ointments—Keeney and his colleagues describe the study of propionate propionic acid and undecylenate undecylenic acid ointments in the treatment of *tinea pedis* and make an *in vitro* comparison between their fungistatic and antibacterial effects with those of other ointments. They state that a compound used in the treatment of cutaneous mycotic infections must be fungistatic, must have penetrating powers and must not sensitize. Using the agar cup plate technique the authors showed that propionate-propionic acid ointment prepared in a Carbowax base was superior in its fungistatic effects upon *Trichophyton mentagrophytes* and in its antibacterial effects upon *Staphylococcus aureus* and β haemolytic streptococcus to undecylenate undecylenic acid ointments, Whitfield's ointment and 5 per cent sulphathiazole ointment. The authors clearly demonstrate in these experiments that sodium propionate and propionic acid and undecylenic acid are the active agents in the ointments. In clinical trials, of which the subjects were 120 midshipmen of the United States Naval Academy, the patients all showed clinical and laboratory evidence of *tinea pedis*. Keeney and his colleagues state that it was not possible to show the superiority of either ointment, but if clinical scaling is removed from the data, the propionate ointment was significantly superior in efficacy. The authors conclude that both ointments satisfy the criteria necessary for the successful treatment of *tinea pedis*, and owing to its *in vitro* superiority they recommend the use of propionate propionic acid ointment, and stress that in the treatment of *tinea pedis* the use of keratolytic agents, foot hygiene, and the wide opening of the vesicular lesions on the soles are valuable adjuncts.

Monilial infections

Clinical picture

Atiologial considerations of perlèche—Finnerud discusses the nosologic position of *perlèche*—a maceration with transverse fissuring of the oral commissures—which usually has been regarded as a disease entity of infectious origin. The causative organism has been variously claimed as streptococci, staphylococci and monilia. Identical cutaneous changes have been repeatedly demonstrated in vitamin deficiency states, chiefly in *ariboflavinosis*, as well as in nicotinic acid and pyridoxine deficiencies. Similar fissuring of the oral commissures occurs in people with malocclusion resulting from ill fitting dentures and in elderly persons in whom tissue atrophy has caused overhanging of the upper lip at its lateral margins. From his own observations and from study of the literature Finnerud concludes that *perlèche* should be regarded, not as a disease entity, but as a cutaneous symptom in the form of an intertrigo of the labial commissures, analogous to intertrigo elsewhere, and of manifold

aetiology. Transverse fissuring is a usual feature in this localized dermatitis, resulting from the frequent movement at the mucocutaneous junction of the lips. Some facts suggest that perlèche epidemically or endemically occurring may be the result of malnutrition, any micro-organisms found being merely secondary invaders thriving on a suitably prepared soil. The term perlèche, derived from the French *pourlécher* (to lick about) should be retained, rather than that of angular stomatitis, interlabial dermatitis or any other term by which the condition has since been designated; the term, however, should be qualified in each instance according to the apparent aetiological factor by a descriptive adjective, such as infectious, mechanical or vitamin deficiency perlèche, or as idiopathic perlèche when no aetiological factor can be determined.

Dermatophytides

Treatment

Application of phenol-camphor.—Phillips discusses the treatment with phenol-camphor of 230 proved cases of dermatophytosis among soldiers and members of the Auxiliary Territorial Service. Equal parts of pure phenol and camphor were mixed and when liquefied were applied to the right side of the body only, the left side being treated with a control preparation consisting of Whitfield's ointment containing 0.5 per cent dithranol. The patient was put to bed, washing of the affected areas was not allowed; the scales were removed and the skin was swabbed dry before each treatment. The control ointment was applied twice and phenol-camphor 4 times daily, in the latter case the skin being left to dry for one hour before the part was covered again with bedclothes. Treatment was continued until all scaling had ceased and the skin had become smooth and non-irritating. Patients then returned to duty and reported at weekly intervals for 3 months when, if relapse had not occurred, cure was considered to be proved. Although all cases responded to treatment within 13 days, for statistical purposes a limit of 9 days' treatment was fixed. During this time, out of the 230 cases 5 failed to respond to phenol-camphor and 17 to the control. In addition, 4 relapses after application of phenol-camphor and 14 relapses after that of the control preparation occurred during the 3 months' follow-up. The possible toxicity of phenol-camphor was investigated by a general relaxation of precautions during its trial in this series, until the last patients were given ambulatory treatment and were allowed to dress immediately after each treatment. No evidence appeared to support the theory that phenol-camphor when applied to wet skin will cause burns, and there were no cases of general toxicity. In 4 cases only, all of tinea cruris, erythema and vesication developed after repeated applications, whereas in 32 control cases vesication was present. Phillips concludes that phenol-camphor is clean, easy to apply, non-staining and non-irritating. No evidence of toxicity was found in the method described and it should prove to be a specific method of treatment of dermatophytosis.

Finnerud, C. W. (1944) *J. Amer. med. Ass.*, 126, 737.

Keeney, E. L., Ajello, L., Broyles, E. N., and Lankford, Elsie (1944) *Johns Hopk. Hosp. Bull.*, 75, 417.

Phillips, B. (1944) *Brit. J. Derm.*, 56, 219.

GALL-BLADDER AND BILE-DUCTS

See also B.E.M.P., Vol. V, p. 477; and Cumulative Supplement, Key Nos. 545-550.

Physiology

Secretion of bile

Cholagogues and choleretics.—McGuigan states that, although the secretion of bile has been studied for 2,000 years, its complete function is not yet understood. The amount of bile actually secreted by the liver cannot be accurately measured, not even through a fistula, because normal conditions are not present. A cholagogue is any agent that will increase the biliary flow. A choleretic is a drug that increases the secretion of bile, just as a diuretic increases the subnormal flow of urine. There is a maximum rate of the flow of bile in a 24-hour period. The giving of a drug will not increase this maximum. Only a subnormal amount of secretion, as in constipation, can be increased. Bile itself is not a choleretic, although many authorities state that it is. Bile salts administered are excreted without causing any additional secretion of bile. It can be shown that bile has an anticholeretic action, diminishing the normal formation of bile in the liver. Administration of bile or bile acid salts gives the appearance of a "choleresis", but there is no evidence of increase of bile acid secretion. When constipation causes a decrease in the flow of bile, administration of bile or bile salts will prove to be beneficial in treatment.

Gallstones

Incidence

Aetiology of gallstones.—According to Robertson, one of the few points of common agreement amongst authors of studies on gallstones is that these occur more often in women than in men. He discusses the preponderance, analyses the chief theories of the causation of stones, and points out the fallacies inherent in the statistical argument that pregnancy is an aetiological factor. Quoting observations that abnormal bile stasis, resulting from calculus lodged in the cystic duct or carcinoma or stones in the common bile duct, neither produces nor conduces to gallstone formation, the author considers that stasis does not cause gallstones. Paracelsus, in his *Opus Paramirum* published in 1572, stated that "now however the

bile contains this same Tartarum, and it thus happens that in the bile lies the material for stones", with this statement in mind Robertson analyses the various theories of gallstone formation based on changes in bile, and comes to the conclusion that gallstones are composed of the normal elements of the bile which have undergone irreversible sedimentation and the insoluble elements which have become congealed into corporate masses bound together by some tenacious substance. He considers that, although micro-organisms may, theoretically, by agglutination form clumps which act as nuclei for the aggregation of precipitated cholesterol and bile pigments, there is little evidence that micro-organisms play any major part in gallstone formation. Both associated diseases and constitutional susceptibility have been invoked in discussing the aetiology of gallstones. It seems to have been clearly established that diabetics, females especially, are prone to suffer from gallstones and that, in the average case, cholelithiasis has been diagnosed at least 12 years before the onset of diabetes, some authorities have inferred that gallstones cause diabetes. The two diseases, the author suggests, may be produced by the same factors, or complications of gallstones, such as infection or injury to the liver, may be effective in causing diabetes. The ancient doctrine of the predisposition of the "fair, fat and forty" to gallstones is questioned and hereditary or constitutional predisposition is considered to be non proven. Robertson concludes that "gallstones occur only when there is a profound disturbance of biliary physiology induced by pathological deviations of hormonally controlled functions", and quotes Schenk as stating in 1644 that "gall stones, acting secretly, make us to be ignorant of the cause".

Cholecystitis

Aetiology

Part played by bile cholesterol—Womack, in discussing the aetiology of cholecystitis, draws attention to the tendency to regard bacterial infection as the sole cause of inflammation. The clinical features of cholecystitis do not always bear out this belief, for instance bacterial infection of the portal system is much more common in children and in adolescents, yet cholecystitis occurs chiefly in older people, particularly women, and in its acute stage is almost always associated with blockage of the bile duct and with the presence of gallstones. Andrews and Henry examined cultures from the walls and bile of diseased and normal gallbladders and showed that the bacteriology varied very little and that in some cases cultures from diseased gallbladders were sterile. Womack, experimenting with dogs, found that if the gallbladder drained of bile before complete obstruction of the cystic duct was produced inflammation did not occur, whereas if bile was left in the gallbladder before the duct was blocked, inflammation and even necrosis of the wall resulted. These results are borne out by the histological examination of 354 diseased gallbladders in human beings, 32.8 per cent of which showed evidence of lipid or bile reactions in their walls. The conception that bile cholesterol may be the cause of inflammation would mean that cholesterosis or "strawberry" gallbladder could be regarded as an early stage of cholecystitis and would also link the disease with the formation of gallstones. This aetiology would be consistent with the clinical features of the complaint.

Cholecystography

Use of Priodax—Vaughan and Eichwald report on the use of Priodax (phenodol) a contrast medium for cholecystography. It was first used in Germany under the name of Biliselectan and was favourably reported on in the literature as being less toxic in its effects than was sodium tetraiodophenolphthalein (iodophthalein). Priodax is a white, odourless powder, sodium salt it is, however, easily soluble in water. It contains 51.5 per cent iodine. Priodax is each, 3 grammes being the average adult dose. In 163 unselected consecutive cases three methods of oral administration were used: a double, a divided and a single dose, the toxic butter at noon and 6 tablets after a fat free meal at 6 p.m., on the day before examination, which took place at 8.30 a.m. By the second method, 3 tablets were given before and 3 after the evening meal, and by the third method, 6 tablets were given after this meal. Good concentration of dye was found in 126 cases and the gallbladder was never obscured by unabsorbed dye. Diarrhoea, nausea and vomiting were infrequent. A second series of 63 patients were analysed, of whom 24 presented evidence of disease. There was thus a total of 22 cases of gallbladder disease correctly diagnosed and verified by cholecystectomy, out of 226 examinations. Gallstones were demonstrated in other cases but the diagnosis was not confirmed by cholecystectomy. The single dose technique was considered to be the most satisfactory.

Dietetic considerations—In a paper read before the Massachusetts Medical Society, Alvarez questions the scientific value of the medical treatment of cholecystitis current in the United States of America—a diet low in fats and a prescription for some preparation containing bile salts or bile salts with a laxative such as phenolphthalein—and pleads for a more thoughtful consideration of its rationale. Fats in the diet should be avoided only if the patient finds himself to be more comfortable without them. Actually, in all cases of cholecystitis without jaundice, bile flows freely from the liver into the duodenum, and the cholecystogram shows the gallbladder to be working fairly well. An imperfect digestion of fats would cause diarrhoea.

with fatty stools and loss of weight, but in fact patients usually digest well and gain weight. It has been shown that fats such as cream and egg yolk cause the gallbladder to contract more forcibly and therefore to empty itself. To avoid fat is to invite stagnation of bile in the gallbladder, which favours the formation of stones. It has been found that the giving of bile salts increases the flow into but not out of the gallbladder. Cholecystitis has a tendency to remissions lasting for many years during which no treatment is required, but when the patient has much pain and flatulence, when bile has ceased to flow easily into and out of the gallbladder, or when that organ is full of stones or its wall is diseased and full of bacteria, the only rational treatment is surgical.

Pitfalls of cholecystectomy.—Simon enumerates the many pitfalls to be avoided in cholecystectomy. These mistakes arise from inexperience in a difficult operation and from failure to recognize anatomical variations and abnormalities which are most frequent in the region of the foramen of Winslow. Ligature by mistake of the common duct, hepatic duct or hepatic artery will be followed by disaster to the patient. These are all deeply situated under the liver and may not easily be identified because of difficulty of exposure to direct view. The surgeon must bear in mind the numerous variations in anatomical structure and relationship of the various ducts and arteries. Variations are so numerous that it is difficult to determine what the normal anatomy is. In 12–18 per cent there are 2 cystic arteries. The variations may be further complicated if pathological changes are present leading to distortion. The cystic duct is not at the bottom of the gallbladder but at the inner side and its pelvis may overlap the cystic duct, which varies in length, and may also cover the common duct above the duodenum. The junction of the hepatic, cystic and common ducts is the all-important area to expose clearly to view. Bleeding is likely to obscure the view, and if it occurs the hepatic artery must be digitally compressed and the bleeding-point sought for and secured. A clamp blindly applied may include the hepatic duct, with irremediable consequences. As a means of avoiding mistakes, it is recommended to dissect the gallbladder from the fundus downwards to the cystic duct. If the loosened gallbladder is gently pulled upon, variations of ducts and arteries will be disclosed which can be more easily identified when dense adhesions have been dealt with. It is essential to drain after cholecystectomy on account of the possibility of accessory bile ducts.

Carcinoma of the gallbladder

Aetiology

Cholelithiasis and primary carcinoma.—The relationship of cholelithiasis to the causation of primary carcinoma of the gallbladder is stressed by Finney and Johnson. They point out that carcinoma of the gallbladder is more common than general practitioners believe it to be, that its prognosis is very bad, and that treatment lies in its prevention by early cholecystectomy of a calculous gallbladder. When such a condition is diagnosed, even if it is quiescent, cholecystectomy should be performed. The sooner the operation is carried out the better, for it is thus possible to make carcinoma of the gallbladder a preventable disease. Since every abdominal surgeon is aware of this possible sequel to cholelithiasis, he should advise early cholecystectomy. Further reasons for early operation are the degenerative effects of chronic cholelithiasis on cardiac muscle and coronary arteries and the disturbances of gastrointestinal functions. Necropsy records reveal that 8–10 per cent of all cancer occurring in the female is primary in the gallbladder and of those dying from this disease 75–80 per cent are found to have coexisting cholelithiasis. It is computed that in 4–5 per cent of all calculous gallbladders carcinoma eventually develops. An analysis is presented of 18 cases, 2 male and 16 female patients, one of whom was under 50 years of age, one over 80, and the others between 50 and 80 years old; the average age was 67·4 years. The presence of gallstones was proved in 11 cases. There was a history in 2 cases of previous removal of stones with drainage of the gallbladder, and in these malignancy also involved the drain tract from the gallbladder to the abdominal wall. Thirteen patients died in less than 6 months after the operation and 15 in less than a year. In 2 cases early carcinoma was found microscopically but both of the patients died from malignant recurrence, one 16·5 months and the other 25 months after the operation.

Diseases of bile ducts

Stone in common bile duct

General surgical principles.—In a paper on surgery of the common bile duct, Fowler points out that success depends upon familiarity with the detailed anatomy and upon the experience of the surgeon. Traction on the duct should be avoided and fine needles and suturing materials are required. In resection of the duct, unless a vitallium tube is used the cut should be oblique in order to prevent contractures. T-clamping of the cystic duct avoids the entrance of small stones into the common duct. Identification is usually simple unless there is a deviation from the normal relationship of the parts. When choledochus stone is suspected, exploration of the common duct should be carried out as soon as the patient can have the necessary preparation (vitamin K and glucose). Stones can be identified by probing through the cystic duct and by digital examination; if there is any doubt, the common bile duct should be opened. Resection and end-to-end anastomosis is possible if accurate approximation can be obtained without tension. A T-tube, catheter or vitallium tube may be used for reconstruction. Choledochoduodenostomy or hepaticoduodenostomy may be done immediately or after preliminary duct drainage has been carried out. An external biliary fistula of the common duct may be

transplanted into the stomach or intestine Postoperative choledochography through the T-tube may be useful Non-inflammatory cases are drained through a large cystic duct, inflammatory cases require longer drainage with irrigation of the ducts through the T-tube When the tube can be clamped off for a week without symptoms, it may be removed If a sudden stoppage in drainage is accompanied by jaundice and irrigation fails to relieve the condition, choledochography may show the site of obstruction After cholecystectomy, attacks of pain similar to the original ones sometimes occur and usually may be relieved by diet, if they are due to overlooked stones in the common duct, prolonged T-tube drainage with thorough exploration will result in relief, provided that the sphincter of Oddi admits a medium sized probe

- Alvarez, W C (1944) *New Engl J Med*, 231, 781
 Finney, J M T, Jun, and Johnson, M L (1945) *Ann Surg*, 121, 425
 Fowler, R S (1944) *Amer J Surg NS*, 68, 15
 McGuigan H A (1944) *Amer J digest Dis*, 11, 282
 Robertson, H E (1945) *Surg Gynec Obstet*, 80 *Intern Abstr Surg*, 1.
 Simon, M M (1944) *Amer J Surg NS*, 66, 367
 Vaughan, W W and Eichwald, M (1944) *Radiology*, 43, 578
 Womack, N A (1944) *Surg Gynec Obstet*, 79, 441

GAS GANGRENE

Treatment

Penicillin

Cutler and Sandusky discuss the treatment of clostridial infections with penicillin Experimentally penicillin has been shown to have a bacteriostatic effect upon organisms associated with gas gangrene, but little is yet known of its clinical value in this condition The authors discuss in detail the treatment of 7 cases of gas gangrene, in 6 of which the condition developed after wounds incurred in aerial warfare In all cases compound fracture of one or more of the bones in the lower limbs was present with much bleeding and damage to muscle tissue In 5 cases the patients were in a state of profound shock and needed large plasma and blood transfusions but in no case was the interval between injury and treatment more than 12 hours Penicillin was given prophylactically at the initial operation locally and parenterally in 5 cases and when the infection was diagnosed in the other 2, administration was continued after diagnosis in all cases Primary surgical treatment consisted in thorough debridement and irrigation of the wound in all but one profoundly shocked patient Prophylactic gas gangrene antitoxin was given in only one case but therapeutic doses were given in 6 cases after discovery of the infection Clostridial infection was discovered 23–60 hours after injury and amputation of the limb was necessary in 5 cases One patient died from uraemia The authors find it difficult to estimate the exact value of any of the several factors which contributed to the successful outcome of the treatment contrary to the conclusions reached in previous reports to which they had had access Cutler and Sandusky do not consider that penicillin used prophylactically prevented the onset of gas gangrene in the above cases This series, however, does not provide sufficient evidence to estimate the exact value of penicillin and the authors believe that surgical debridement is still the greatest factor in both the prevention and the treatment of gas gangrene infections

Cutler, E C, and Sandusky, W R (1944) *Brit J Surg*, 32, 168

GASTRITIS

See also B E M P, Vol V, p 533, and Cumulative Supplement, Key No 558

Diagnosis

Chronic gastritis

Review of diagnostic features—In the course of a discussion on gastritis, Bennett stresses frequent absence of symptoms lack of knowledge of aetiology, doubtful prognosis and the certainty that there is no effective treatment He cites Wolf and Wolff's important observations on a man with a permanent gastrostomy into whose stomach the introduction of air under pressure not exceeding that sometimes reached during gastroscopy was sufficient to flatten out the mucosa entirely, and produced the appearance of "so-called atrophic gastritis" Jones describes illustrative cases and suggests various classifications but concludes that the final proof in diagnosis of gastritis must be histological and that correlation between gastroscopy and histology has not been achieved Cordiner describes radiological investigation by coating the gastric mucous membrane with a thin layer of contrast medium, but concludes nevertheless that there are no characteristic findings which enable the radiologist to diagnose atrophic gastritis Hancock considers that the only types of chronic gastritis having a recognizable syndrome are alcoholic and chronic diffuse atrophic gastritis that radiology is of no assistance in diagnosis and that gastroscopy offers the only means of positive diagnosis, provided that allowance is made for normal variations Gill thinks that reliable conclusions can be drawn from combined gastroscopic and secretory investigations but suggests abandoning the diagnosis, chronic gastritis for purely descriptive terms such as mucosal hypertrophy, mucosal atrophy and mucosal hyperaemia Tidy emphasizes the fallibility of conclusions drawn from gastroscopy and cites Wolf and Wolff's demonstration

of the changes produced in gastric mucosa by slight physical and nervous stimuli. Spira offers a classification of chronic gastritis for the purpose of clarifying conceptions of gastric pathology. Tanner, analysing 2,200 gastroscopies performed at St. James's Hospital, London, on 1,730 patients, considers that under 4 per cent of the patients had reasonably well marked or chronic gastritic changes which might be considered to be a possible cause of the symptoms. Marshall stresses the importance of muscular involvement and the relative silence of the mucosa. He classifies chronic gastritis either as primary or as secondary to other gastric conditions, notably ulcer, simple or malignant. He contends that muscular involvement is the main cause of gastric pain and thinks that mucosal gastritis with gross structural changes may be symptomless.

Bennett, T. I., Jones, F. A., Cordiner, G. R. M., Hancock, P. E. T., Gill, M., Tidy, H., Spira, J. J., Tanner, N. C., and Marshall, C. J. (1944) *Proc. R. Soc. Med.*, 38, 81.

GLANDULAR FEVER

See also B.E.M.P., Vol. V, p. 559; and Cumulative Supplement, Key No. 561.

Differential diagnosis

From infectious mononucleosis

Value of heterophil antibody reaction.—Rubenstein and Shaw discuss the value of the heterophil antibody reaction in differential diagnosis between *Brucella abortus* infection and infectious mononucleosis. The test was performed on 1,000 consecutive blood sera submitted for *Brucella abortus* agglutination tests; for this disease 36 were positive and 13 revealed the presence of infectious mononucleosis. The authors give details of 6 cases which demonstrated either special similarity between the two diseases or unusual features of one or other condition—notably central nervous or gastro-intestinal system involvement in mononucleosis—of one case of malignant type of brucellosis and of another complicated by epididymitis. They emphasize that this last condition may be the first and only sign of brucellosis; that it may be confused with tubercular epididymitis and that when much raw milk is consumed this complication may be more common than is generally realized. It is stressed that a positive agglutination test may indicate either present brucellosis infection or previous exposure to it, that, apart from splenomegaly, physical signs, in brucellosis, may be few, and that sore throat and lymphadenopathy suggest infectious mononucleosis. One case of brucellosis especially Rubenstein and Shaw cite as of "extreme interest". A 5-year-old child displayed high and intermittent fever, distinct splenic and hepatic enlargement, prostration, leucopenia with lymphocytosis and protracted course, signs all of which are rarely combined in one case. The disease, too, is rare in children though it is fairly common in young adults. The authors emphasize the help in diagnosis afforded by epidemiological observations, and point out that failure to trace infection either to consumption of raw milk or to contact with infected animals or animal products may lead to abandonment of the diagnosis of brucellosis. They mention that infectious mononucleosis is chiefly a disease of children and young adults, that, except in the Forces, epidemics have not occurred in groups over college age, and that, during an epidemic, resistance to infection amongst older people may be striking.

Treatment

Arsenic

Successful use intravenously in anginose type.—Smith and Shaw describe the successful employment of arsenic in the treatment of 6 cases of anginous glandular fever. The drug was chosen for the first case with the aim of countering a Vincent's infection. Each patient was given one intravenous injection of either Novarsenobillon (neoarsphenamine) or sulpharsphenamine, the dosage varying from 0.15 to 0.45 gramme. Speedy and conspicuous benefit was obtained, but one patient required a second injection to complete the treatment. The injections produced a rapid subsidence of the fever and of the throat condition. The apparent effect did not extend to other manifestations such as enlargement of the spleen or lymphatic glands. Furthermore, the Paul-Bunnell titre continued to rise in one instance. Microscopical evidence of Vincent's infection was found in 3 cases, but the response to arsenic in the other cases was similar in kind and degree. The swelling and ulceration of the throat was not relieved by gargles. However, swabbing with hydrogen peroxide was the most effective local treatment in the acute stage. The residual ulceration of the tonsils was treated with a paint—equal parts of solution of arsenic and tincture ipecacuanha. Neutropenia was present in all cases at some stage of the disease, but bone marrow smears showed an approximately normal degree of cellularity. It is considered that sulphonamides are contra-indicated in glandular fever, since these drugs may increase the degree of neutropenia. The important feature in the blood cytology was a departure from normal in a direction other than the absolute neutrophilia which it would have been reasonable to expect in a severe septic throat. This finding prompted further examinations of the blood in order to determine the maximum mononuclear cell increase. The authors conclude that the neutropenia probably plays a secondary part and is not in itself the cause of the faucial ulceration.

Rubenstein, A. D., and Shaw, Carolyn I. (1944) *New Engl. J. Med.*, 231,

111.

Smith, K. S., and Shaw, T. H. (1945) *Brit. med. J.*, 1, 581.

GLAUCOMA

See also B E M P, Vol V, p 575, and Cumulative Supplement, Key Nos 562-565

Primary glaucoma

Treatment

Angiodiathermy of the long posterior ciliary arteries—Guerry describes the effect of angiodiathermy of the long posterior ciliary arteries. Coagulation of a single artery in the anesthetized rabbit's eye produced a rapid fall of tension to half the pre-operative level, the tension remained low for several days and rose slowly to the pre-operative level in about 14 days after the operation. Coagulation of both vessels produced variable results, 5 out of 12 eyes reacted as above, but in 5 in which the cornea showed gross clouding postoperatively, the tension was too low to measure and the eye eventually became phthisical. The microscopical pathology is described in detail and except for irreversible damage to the retina and choroid at the site of treatment, the author concludes that in a rabbit's eye coagulation of a single artery leads to reversible and minimal damage. In 2 out of 3 rabbit's eyes angiodiathermy combined with cyclodiathermy caused a more rapid fall to hypotonic levels after the initial rise than did cyclodiathermy alone. A surgical technique of angiodiathermy of the nasal long posterior ciliary artery in man is described. In 2 cases of absolute glaucoma a rapid and significant drop in tension occurred after coagulation of this artery, in one the level dropped to $\frac{1}{2}$ of the pre-operative level and in the other the level remained low until the fourteenth day and then began to rise, to regain the pre-operative level on the nineteenth day. In a case of diabetic bilateral haemorrhagic glaucoma cyclodiathermy was performed on both eyes, in one combined with angiodiathermy. Tension curves showed that the combined operation caused a more rapid and marked fall in tension. Guerry concludes that coagulation of a single long posterior ciliary artery will cause a transitory reduction of tension in the rabbit's and in the human eye, that it is an innocuous procedure in the rabbit's eye, but that the number of cases in human beings in which the procedure has been carried out is too small to allow of positive conclusions to be drawn.

General review—Chandler considers the treatment of glaucoma in the light of his experiences. Discussing how long miotics should be used in order to try to reduce the tension in acute primary glaucoma, he states that he believes that if the attack is of 24 hours' duration or longer, operation should not be deferred for more than 5 or 6 hours unless tension is certainly lessening. Operation, too, should not be long delayed if vision is down to counting fingers at a few feet. In a vulnerable eye immediate operation is indicated if vision has fallen to hand movements. The author believes that if the tension returns to the normal with the use of miotics, except in the case of older people operation is called for, since without surgical treatment the subsequent history of these patients is invariably of further attacks, each causing still more loss of vision. Treatment of chronic glaucoma must be planned for the purpose of maintaining vision throughout the remainder of life. Admission to hospital at the start for detailed tension studies and the effect of miotics of different strength is often helpful. Chandler believes that few patients with an expectancy of life of 20-30 years can have glaucoma held in check by miotics alone and therefore those in good health who are under 60 years of age should have surgical treatment, this is also advisable in patients between 60 and 70 if strong miotics are necessary. In older patients the indications for operation must be relatively stronger owing to the subsequent almost invariable development or worsening of lens opacities after operation. Surgeons should be guided by their experience in the choice of operations in chronic glaucoma. The author favours trephining in the case of most younger patients, and in older patients iridencleisis. In the treatment of glaucoma secondary to acute iritis he continues the use of mydriatics and tries first a 1 or 2 per cent solution of epinephrine (adrenaline) bitartrate, if this fails paracentesis is tried and if the tension has not lessened within a few hours an incision is made subconjunctivally with a keratome, which produces an exceedingly small cut in the conjunctiva 7 or 8 millimetres from the limbus to a point about 1.5 millimetres from it and then into the anterior chamber (Reese incision).

Chandler, P A (1944) *Arch Ophthalmol* N Y, 32, 23

Guerry, D, III (1944) *Amer J Ophthalmol* 27, 1376

GOITRE AND OTHER DISEASES OF THE THYROID GLAND

See also B E M P, Vol V, p 599, and Cumulative Supplement, Key Nos 569-574

Toxic goitre

Clinical picture

Frequency of occurrence of cardiovascular symptoms—Fitz describes the study of a group of 33 patients with toxic goitre who underwent periodic health examinations, were all thought not to have a toxic goitre when first examined and many of whom were observed for some years after the disease developed. Three of the patients were men. The range of ages was 15-65 years, height from 4 feet 11 inches to 5 feet 8 inches and weight 103-214 pounds. The writer knew details of the patients' lives and health and only in one case would have suspected a predisposition to thyroid disease. Four patients had a family history of goitre, 7 had palpable thyroid glands even when they were not toxic, 13 had presystolic murmurs, 9 had a systolic blood pressure of over 140. Nevertheless there is not sufficient evidence to show that these factors present in one individual presuppose incipient toxic goitre and the actual cause in these cases is not known. In 28 cases the disease developed insidiously, in 6 suddenly

the drug acts by inhibiting the synthesis of thyroxine, to which the organism responds by an increased secretion of pituitary thyrotrophic hormone leading to increased hyperplasia of the thyroid gland. Caution is therefore essential when pressure symptoms already exist.

Routine of thiouracil administration—Eaton describes the beneficial effect of thiouracil in a series of cases of thyrotoxicosis. He believes the treatment to be effective in toxic adenoma, in cases which have recurred after thyroidectomy and in thyrotoxicosis during pregnancy, as well as in the primary type. Three patients with coexisting diabetes responded satisfactorily. The maximum dose of thiouracil required was 800 milligrams daily, with 200 milligrams as a maintenance dose. In one case of pregnancy, in which the patient received the drug until confinement, the child had an enlarged thyroid gland but no clinical evidence of over-activity or under-activity of the gland. Eaton considers that thiouracil should be replaced by iodine in pregnancy cases some weeks before delivery. His findings generally agree with those of other observers, notably in the delayed response to thiouracil seen after previous iodine therapy, the occasional enlargement of the gland occurring under treatment and the absence of toxic effects from the drug when it is given in moderate doses. The author records only one case of transient granulocytopenia in 36 cases but draws attention to the fall in the leucocyte count which occurs commonly early in treatment but which is not persistent. It has been possible to stop all treatment in 4 cases for 8 months and in 3 others for over 3 months without recurrence of symptoms, the average duration of treatment of these 11 patients was 4 months. Most of the patients were allowed to continue their ordinary work as soon as the pulse rate and the basal metabolic rate approached the normal, unless there was appreciable cardiac damage or unless other complications existed.

Aim of thiouracil treatment—Dunlop reviews experimental findings concerning goitrogenic substances. The present opinion is that thiourea derivatives act directly on the thyroid gland—probably by an anti enzymic action—to prevent iodination of tyrosine and thus interfere with the thyroxine synthesis, and that the resultant compensatory increased production of pituitary thyrotrophic factor stimulates thyroid hyperplasia. In treating thyrotoxicosis with thiouracil the aim is to decrease the thyroxine synthesis to the normal limit. Of 31 patients treated by Dunlop with initial doses of 0.6 gramme daily for a period of 3–4 weeks, the great majority showed remission of thyrotoxic symptoms. After a latent period of about 10 days, the basal metabolic rate began to fall, usually reaching normal limits in from 18 to 26 days after commencement of the initial dosage, the dose was then reduced to 0.2 gramme daily. An average gain in weight of 4 kilos was noted during the month's treatment in hospital. Of 39 patients treated with thiouracil by Dunlop and Davidson, 34 have been able to resume their ordinary activities for periods varying from 2 to 11 months. Thyroidectomy was performed in the case of 3 patients who had persisting fibrillation, the procedure did not restore normal rhythm, but administration of quinidine proved to be effective. One of these patients appeared to be resistant to thiouracil, and another required thyroidectomy because leucopenia developed on the twelfth day and sensitivity reactions were manifested to subsequent test doses of the drug. Frequent leucocyte counts are necessary during the initial period, if the count falls below 3,000, thiouracil should be discontinued. There is little danger of toxic reaction or overdosage on the maintenance dose, probably 0.1 gramme will prove to be sufficient, but it is not yet possible to state whether or not administration of thiouracil may eventually be discontinued.

Thiouracil and thyroid substance—Palmer discusses the value of thiouracil in treatment of toxic hyperthyroidism. Fifty unselected cases of thyrotoxicosis were kept under observation at University Hospital, Baltimore. Eighty per cent of the cases were women, and the physical states included young thyrotoxic patients in good condition and patients with longstanding severe thyrotoxicosis accompanied by extensive parenchymatous visceral damage. No serious complications were caused by treatment with thiouracil during a period of from 1 to 10 months and no drug intolerance, idiosyncrasy, or refractoriness was found. Transient leucopenia was the only serious effect, but this might have represented an early step in the development of agranulocytosis, unless frequent blood examinations were made. Every case responded to thiouracil in some measure, but some did so much more than did others. The response was especially notable in cases with a high initial metabolic rate. All cases improved at first subjectively, and then objectively, and it was considered that administration of vitamins and sedatives and the enforcing of rest increased the efficacy of the drug. Although no case required operation, thyroidectomy was performed in certain instances because of economy or convenience, or for cosmetic reasons. Microscopically, varying degrees of hyperplasia and colloid content were found in thyroid glands treated with thiouracil. The effect is believed to be caused by depression of normal enzyme reactions of tissues in general, but especially of the hypophysis (leading to suppression of synthesis of thyroid stimulating hormone), and of the thyroid gland (leading to the inhibition of iodine uptake). More than half the number of cases, according to the degree of exophthalmos present, were given from 1 grain of desiccated thyroid to $\frac{1}{2}$ grain of thyroxine daily, without causing any inhibition of the thiouracil effect. On the contrary, thyroid substance given with thiouracil brought about restoration of normal endocrine balance more quickly and completely, and with less frequent unpleasant side effects than did thiouracil given alone. Four patients, observed for 8 months, have required no medication of any sort for 3 months, and appear to be in normal physiological equilibrium with basal metabolic rates in the range of ± 12 per cent. Patients who

have relapsed because treatment was discontinued too soon, or because of intercurrent infection or emotional stress, have responded as satisfactorily to a second treatment with thiouracil and thyroxine as they did to the first. The cyclic nature of toxic goitre must not be forgotten, and remissions obtained by any treatment must not be confused with cures. A small number of cases have been successfully tided over one or more exacerbative phases. Some cases have escaped requiring thyroidectomy because a responsible focus of infection has been found and removed, but such cases are few and the risk of operation in an uncontrolled thyroid state is grave.

Thiouracil used pre-operatively.—Clute and Williams report their experiences in treating 115 thyrotoxic patients with thiouracil, with special reference to its value in preparing patients for surgery. In 81 cases thiouracil alone effected reduction of basal metabolism to the normal, remission of toxic symptoms and gain in weight. Iodized patients responded more slowly. The authors' present opinion is that thyroidectomy in addition to thiouracil medication is indicated for patients who have very large goitres or who cannot attend for frequent examination or who are uncooperative. Single discrete adenomata require immediate removal. Pre-operative preparation consists of daily dosage of 0.6 or 0.4 gramme of thiouracil for 5 or 6 weeks, by which time in an average patient the basal metabolism will have become normal. These patients report at least fortnightly so that metabolism and blood tests may be made. Exceptionally toxic cases and thyrocardiacs require to be in hospital throughout the pre-operative period. The anaesthetic, operative and postoperative courses in patients adequately prepared with thiouracil were strikingly uneventful. More bleeding, however, was encountered in some of these cases than in cases treated with iodine. Histologically, thyroid glands treated with thiouracil showed very little colloid. Thiouracil was discontinued 4-6 days after operation. In 2 patients urticaria, joint pains and fever necessitated withdrawal of thiouracil. In patients with malignant exophthalmos the minimal effective dose to reduce metabolism should be given. Metabolism has remained normal in 33 of the 34 operated cases reported on. Satisfactory response to thiouracil was obtained in 15 patients with persistent or recurrent toxicity after thyroidectomy.

The use of thiouracil as a preparative drug for the procedure of thyroidectomy is discussed by Moore, Sweeny, Cope, Rawson and Means. Thirty-four patients were treated pre-operatively with thiouracil and after operation were observed for a time long enough to enable certain conclusions to be drawn. The action of thiouracil in thyrotoxicosis is to reduce the basal metabolic rate and to produce an intensification of hyperplasia accompanied by increased vascularity and friability. From the point of view of the metabolic rate, which is reduced to the normal or lower, the operative risk becomes equivalent to that in non-toxic goitre. In patients prepared with iodine there is usually a residual elevation of the metabolic rate and the operative and postoperative courses of these patients are stormier than is that of those prepared with thiouracil. The entire physiological state does not return to the normal with administration of thiouracil and the endocrine disorder is unchanged; this accounts for the postoperative upheavals which occur in some patients in whom the metabolic rate has been reduced to the normal. The increased vascularity of the thyroid gland may cause difficulty in recurrent haemostasis, particularly in cases in which thyroidectomy has been previously carried out. In thyrocardiacs, who carry the worst surgical risk, the drug acts slowly, but its advantages outweigh the disadvantages of a long preparation with the patient confined to bed. Preliminary or concomitant iodine administration delays the thiouracil response. It is possible that iodine therapy subsequent to thiouracil treatment may reduce hyperplasia and vascularity. Toxaemic symptoms similar to those caused by the sulphonamides may occur during thiouracil treatment.

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Nussey, A. M. (1944) *Brit. med. J.*, 2, 745.

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GONORRHOEA

See also B.E.M.P., Vol. VI, p. 1; and Cumulative Supplement, Key Nos. 575-578.

Gonorrhoea in males

Treatment

With sulphonamides.—Williams, King and Nicol review results of 4 years' treatment with sulphonamides of gonorrhoea in patients in the Forces. Most of the patients were treated with sulphapyridine, a standard daily non-intensive dosage being adopted in the first place. Attempts thereafter were made to vary the intensity of treatment to the point at which it became clear that the compound was ineffective. It was found that the best results with sulphapyridine

were obtained in a 3-day course with a daily dosage increased from 4.5 to 6 grammes. The incidence of intolerance or sensitivity to sulphapyridine fell sharply in course of treatment of less than 7 days. Vomiting and minor toxic effects of the compound occurred in all the series of cases. Immediately haematuria resulting therefrom is diagnosed, 1,000 cubic centimetres of fluid intravenously must be given. When anuria is present this procedure is dangerous, the condition requires catheterization and lavage of the ureters. Sulphathiazole and sulphadiazine were found to be less toxic and are considered to be the drugs of choice in acute gonorrhoea. Patients in whom gonococci are still found in meatus smear after a course of sulphonamides are said to be gonococcus fast, and when the two last-mentioned compounds are used the percentage of gonococcus-fast patients was found to be less than it was with sulphapyridine. In some cases gonococci may disappear from the urethral smear after a course of treatment but the discharge and evidence of infection remain in the patient's urine. In many cases in which gonococci remained after a first course but disappeared after a second, it was found that a provocative injection of anti-typhoid-paratyphoid vaccine would bring about their reappearance. There appears to be reason to suspect that strains of gonococci may be becoming sulphonamide-resistant owing probably to the frequency with which these drugs are prescribed for conditions antecedent to gonococcal infection.

Sulphonamide-resistant gonorrhoea treated with penicillin—Scarcello reviews 200 cases of sulphonamide-resistant gonorrhoea treated with penicillin. All patients previously had had at least 40 grammes of sulphonamides without benefit. On admission to a United States Naval Hospital in Long Island all patients had a positive prostatic or urethral smear. The total amount of penicillin given in the initial course was varied, the optimum appearing to be 5 intramuscular injections of 20,000 units at 2-hourly or 3-hourly intervals. No complications occurred and in over 80 per cent of the cases there was no urethral discharge 24 hours after treatment. Fourteen per cent of patients needed 2 or more courses of penicillin in order to establish a "clinical cure", the criterion for this being 2 negative prostatic cultures and smears. Gonococcal arthritis and prostatic abscess cleared up well under treatment with penicillin, but the substance had no apparent effect upon epididymitis. From an analysis of the cases which required repeated courses of penicillin Scarcello concludes that a large initial dose of 100,000 units or more gives the best results. He considers that negroes do not respond well, since about 50 per cent of the negroes who were treated needed repeat courses. Sulphonamides should be given for as long as possible in order to keep the infection localized. The fact that penicillin therapy obscures the diagnosis of a chancre in its early stages should not be overlooked.

Penicillin—Robinson reports on the results obtained by the treatment of gonorrhoea with penicillin. In 1,000 cases of sulphonamide resistant gonorrhoea the patients were treated with a dosage of 100,000 units of penicillin which were given intramuscularly in doses of either 10,000 units hourly or 20,000 units 3-hourly. Of these, 947 patients were cured within 15 days. In 53 cases the patients required further penicillin treatment. Of these, 30 had only an anterior urethritis and 23 an additional posterior urethritis, only 2 had other complications. Urethral smears were all negative on completion of the first course but subsequently became positive at varying intervals up to 21 days. All patients but 3 responded to administration of further penicillin and 3 responded to a third course. The author discusses the reasons why further penicillin therapy was necessary. Since all the gonococci cultured were sensitive to penicillin, he suggests that the varying sensitivity of different strains of the gonococcus may be an explanation. In 100 previously untreated cases of acute gonorrhoea the patients were given intramuscularly 5 doses 2-hourly and also 3 hourly of 20,000 units of penicillin. Satisfactory response was obtained in 97 and 3 required a second course. The author notes that it appears that primary and secondary syphilis may be inhibited by penicillin therapy and he states that therefore all cases should have monthly tests for syphilis for at least 5 months. Robinson concludes that penicillin is as yet the most effective agent known for the treatment of all forms of gonorrhoea.

Penicillin and the 8-hour scheme in the Royal Navy—Jones, Maitland and Allen present an 8 hour scheme for the treatment of gonorrhoea, which was evolved by using trial doses of penicillin controlled by slide, culture and blood serum inhibition levels. Graphs of bacteriostatic levels of the patients' blood serum, plotted against the time elapsing after the first dose of penicillin, together with a table presenting the results obtained with 7 different schemes of penicillin injection, demonstrate that relapses were relatively frequent in those courses in which a bacteriostatic titre above a serum dilution of 1 in 8 was not maintained for over 8 hours. The scheme finally adopted as routine gonorrhoeal treatment for the Royal Navy consisted of 30,000 units dissolved in 1.5 cubic centimetres of pyrogen free sterile distilled water injected intramuscularly at 2 hourly intervals for 5 doses, namely 150,000 units in 8 hours. Of 265 unselected consecutive cases so treated, only one relapsed, but was cured by a second similar course. The standard of cure attempted was urethral and prostatic smears and cultures 48 hours, one week, one month and 2 months after treatment. Those cured included 26 patients who were sulphonamide resistant, 9 who were failures from other penicillin treatment schemes, and 7 who were having arsenicals and bismuth for concurrent syphilis. Results from a series of *in vivo* and *in vitro* experiments suggested that neither Mapharside, neoarsphenamine nor Bisoxyl, in therapeutic doses, inhibit the bacteriostatic action of penicillin.

Dudley, in a postscript, stresses the immense economy in man-hours and sick-beds that will be effected by avoidance of in-patient treatment.

Essential principles.—McLachlan states the principles underlying the modern treatment of gonorrhoea in the male. These are (1) accuracy of bacteriological diagnosis and of the anatomical part affected, (2) adequate dosage of the selected drug over a sufficient period of time and (3) careful supervision after cessation of symptoms or apparent cure. Chemotherapeutic treatment should not be started until the probable diagnosis is verified by demonstration of the gonococci in smears or in culture made from the urethral secretion. In the meantime a potassium citrate mixture should be prescribed. The anatomical extent of infection is determined by the two-glass urine test. Turbidity of the second glass will show that the posterior urethra is involved. General treatment includes rest in bed, non-stimulating diet with abundance of fluid and regulation of the bowels. Sulphathiazole and sulphadiazine are the best drugs, and the daily dose is 5 grammes, 3 tablets being taken after breakfast, 3 more in the early afternoon and a further 4 before retiring to bed. There is rapid clinical improvement and after 24 hours gonococci cannot be detected in urethral smears. Observations continued over 3 months are needed to justify the assumption of cure. Serological tests for the exclusion of syphilis should not be omitted, since the dual infection occurs in 5–10 per cent of cases. In sulphonamide-resistant cases it may be necessary to try local irrigation with administration of gonococcal vaccine, to induce fever therapy or to administer penicillin. Irrigation of the posterior urethra should be carried out by a gravity douche apparatus and Janet nozzle, supplemented by an initial dose of 0.1 cubic centimetre of gonococcal vaccine followed by a second course of a different sulphonamide. Fever therapy has proved to be of some value but is now displaced by penicillin therapy, of which a dosage of 150,000 Oxford units, in five 3-hourly injections of 30,000 units, is curative.

Gonorrhoea in females

Treatment

Review of modern treatment.—Lloyd describes the modern treatment of gonorrhoea in the female. In pre-sulphonamide days it was a thankless task but now there is a reasonable prospect of achieving a cure in 6 weeks or less. Infection may have spread to the tubes and peritoneum before advice is sought and abscess formation may be the first sign of the infection. Bacteriological investigation is essential for accurate diagnosis and control of treatment. Routine serological tests should be employed. Plenty of fluid should be given along with an alkaline diuretic. Chemotherapy has otherwise displaced older methods of treatment and penicillin has been shown to be effective in sulphonamide-resistant cases. An initial dose of 2 grammes of sulphathiazole is given followed by 1 gramme 4-hourly for 48 hours and afterwards by 1 gramme 6-hourly until 30 grammes have been taken along with 6 pints of bland fluid per day. If intolerance shows itself, the leucocytes must be examined and if the results are satisfactory a 20-gramme course of sulphadiazine is started. Smears are taken from the neck of the uterus and the urethra after completion of the treatment and are examined at weekly intervals for 1 month; post-menstrual smears should be taken for a period of 3 months. Local treatment is now largely abandoned. Insufflation of the vagina, twice in the first week, with sulphanilamide powder may prove to be beneficial. Penicillin, when available, has been used as the only means of treatment and all the results recorded bear testimony to its efficacy. The most widely used form of the drug is sodium salt of penicillin. In vulvovaginitis in childhood, examination should be carried out under general anaesthesia, and discharge from the upper vagina should be obtained for a smear test and for culture. Sulphathiazole in appropriate doses is administered and stilboestrol in doses of 1 milligram 3 times a day for 21 days. Abscess of Bartholin's (greater vestibular) gland requires surgical treatment, culture of the organism and a full course of sulphathiazole.

Penicillin in chemoresistant cases.—Greenblatt and Street describe the results of penicillin treatment of chemoresistant gonorrhoea in patients attending the Southeastern Medical Centre, Oatland Island, Savannah, Georgia. The series comprised 551 females of ages from 3 to 48 years, of whom 54 per cent were negroes and 46 per cent were whites. Although a far greater number, comparatively, of negro than of white women had clinical evidence of gonorrhoea, the diagnosis was confirmed bacteriologically twice as frequently in white women. One hundred and nine patients, of whom 93 per cent had had one course or more of sulphonamide therapy, were treated with penicillin. The dosage was 10,000–20,000 units given intramuscularly at 3-hour intervals until 60,000–150,000 units had been administered; no untoward reactions occurred. Cultures obtained within 12–24 hours after treatment were usually negative. In 9 cases positive cultures were got 24 hours after penicillin had been administered, in 3 after 48 hours, in 3 after 72 hours and in 4 after 96 hours. Positive cultures obtained after the fifth day were considered to be failures, and this occurred in 6 cases. In 5 other cases reinfection occurred, and was overcome by a second course of treatment. Urethral discharge and symptoms of vaginitis, salpingitis and pelvic peritonitis commonly abated within 24–48 hours but, on the other hand, purulent urethral and cervical secretions often continued in spite of negative smears and cultures. The dosage should be maintained at a sufficiently high level; 150,000 units is recommended to be given, although good results can be obtained with 60,000 units, for the purpose of preventing the development of penicillin-resistant strains.

Gonorrhoea in both sexes

Treatment

Penicillin—Riba, Schmidlapp and Bosworth describe the treatment with penicillin of 450 sulphonamide resistant cases of gonorrhoea in males and females. One hundred and five patients received 160,000 units of penicillin (10,000 units intramuscularly 3 hourly), there were 2 failures, one of which responded to intensive treatment with 1,000,000 units. Another 112 were given 100,000 units (10,000 units hourly), there were 11 failures, and administration of 160,000 more units gave 6 additional cures. Two hundred and twenty-three received 100,000 units (10,000 units 3 hourly), there were 55 failures, and 48 of these cleared successfully with re-treatment with a further 100,000 units and 1 with 160,000 units. The treatment was well tolerated. The complication which occurred most often in these patients prior to treatment was acute prostatitis (67.7 per cent of cases). After treatment a great incidence of positive and doubtful smears was found in the first 14 days, but these did not indicate either success or failure. If the doubtful smear persists it is suggestive of failure or that the patient is a possible gonococcus carrier. These doubtful smears were most common in the low dosage group. Positive smears and cultures usually suggest failure. The authors believe that the action of penicillin is bacteriostatic and that when the substance fails to cure, the attenuating influence becomes less between the seventh and the fourteenth days and failures can be missed if post treatment observation is continued for only a few days. Of the 14 cases in which penicillin failed, including 2 in group 1, 12 were treated with hyperpyrexia and 100,000 units given intravenously, there were 4 successes. Six of the remainder were treated with intensive penicillin therapy (1,000,000 units), 3 successfully. Thus of the 68 primary failures 61 were due to an insufficient quantity of penicillin. Of the 7 remaining failures 4 cleared quickly when after urological investigation they were treated with sulphapyridine, urethral irrigations and instillations of silver protein (argentoproteinum). The authors believe that routine massage of foci of infection is part of good urological practice. A total of 160,000 units of penicillin appears to be near the maximal optimum dose necessary to clear the greatest percentage of resistant gonorrhoeal infections in males.

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Lloyd, O. (1945) *Practitioner*, 154, 302.

McLachlan, A. E. W. (1945) *Practitioner*, 154, 295.

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GOUT

See also B. E. M. P., Vol. VI, p. 37, and Cumulative Supplement, Key No. 579.

Treatment

General and spa treatment

Summary of main factors in therapy—Bauer and Klemperer state that specific treatment of gout—a hereditary constitutional disorder—should be based on knowledge of the cause of hyperuricaemia and of factors leading to precipitation of urates in the tissues. Most evidence suggests that hyperuricaemia results from impaired renal excretion of uric acid, this is not the sole cause of urate deposition, however, since gout does not necessarily ensue in renal disease or in leukaemia in both of which increased uric acid formation occurs. Nor, in a given patient, is there correlation between clinical symptoms and fluctuations of serum urate concentrations, because sodium urate tends strongly to remain in supersaturated solution. The serum of gouty patients is probably supersaturated with sodium urate, i.e. the concentration exceeds 6.5 milligrams per 100 cubic centimetres. The physicochemical factors initiating precipitation are unknown but are apparently independent of serum concentration. Owing to the extreme variability in the clinical course of gout and to the little value of serum urate level determinations, evaluation of any treatment is difficult. Acute attacks can be alleviated usually by prompt administration of a total of 4–8 milligrams of crystalline colchicine, 0.5 milligram hourly, until relief is obtained or gastro-intestinal upset results. Pain and swelling usually subside within 24–72 hours after the first appearance of diarrhoea, which is controlled by administration of paregoric. Absolute rest in bed during the attack, hot fomentations locally and liberal fluid intake are helpful. From experience with their own patients and a review of the literature, the authors conclude that treatment during the intervals between attacks with diet or drugs or with both has proved to be disappointing. There is no pertinent evidence that low purine or fat free diets alter the clinical course of the disease or even lessen the incidence of attacks. Temporary increase in urate excretion can safely be effected by administration of salicylates, or of cinchophen, although cinchophen is not recommended, since it is toxic. Acetylsalicylic acid given in continuous daily dosage of 5–6 grammes may temporarily reduce the blood urate even to one third of its original level. Continuous salicylate

medication will not prevent attacks of gout since it is impossible to maintain the serum uric acid level permanently below the critical level of about 6.5 milligrams.

Bauer, W., and Klemperer, F. (1944) *New Engl. J. Med.*, 231, 681.

GRANULOMA, ULCERATIVE

See also B.E.M.P., Vol. VI, p. 54; and Cumulative Supplement, Key No. 580.

Clinical picture, course and prognosis

Nodular dry type

Possibility of a "new" venereal disease.—Cowe describes a special venereal sore ("Middle East Granuloma") which in 6 months occurred about 30 times in 350 other venereal sores. These special sores followed exposure to infection in a particular area (seaport towns) through intercourse with non-European women. Usually by the fourth week after infection there was present a well defined ulceration with marked induration and raised edges of a dark-red to purple colour; the ulcer had a tendency to bleed readily. *Treponema pallidum* was not found and the Kahn and Wassermann reactions were negative. For about 3 weeks the ulcer spread slowly, then reached a static stage. Infection of the base subsided, the ulcer filled in slowly and healing took place in another 10 days; the total period spent in hospital was 6 weeks. The ulcer was painless and seldom caused inguinal adenitis. Ulceration was more extensive in non-Europeans. Bacteriologically the most common finding was an organism resembling *Klebsiella pneumoniae*. It was found that sulphanilamide, when given towards the end of the progressive stage, helped to clear infection and hastened healing. Auto-inoculation from the sore can produce a similar ulcer elsewhere. The sore corresponded in nearly all particulars to the description of granuloma venereum recorded by Greenblatt, including the pathognomonic large mononuclear cells. Whether or not the healing of the ulcer cures the disease is not yet known. The ulcer may be only the first sign of a generalized infection, but it may be a "new" venereal disease.

Cowe, W. R. S. (1945) *Brit. J. vener. Dis.*, 21, 34.

HAEMATOPORPHYRINURIA

See also B.E.M.P., Vol. VI, p. 85.

Biochemical

Types of porphyrins

Porphyrin derivatives are an essential part of the respiratory enzymes present in all living cells. Welcker states that all the porphyrin compounds consist of a basic porphyrin ring made up of four pyrrole groups attached to each other by methylene linkages. Only protoporphyrin, coproporphyrin and uroporphyrin occur in the body. The latter two are found largely in the urine and faeces. Protoporphyrin is found free in erythrocytes and is associated with certain young cells called fluorescytes and with reticulocytes. In diseases in which these cells are numerous the erythrocyte protoporphyrin increases and can be considered to be a supply for the building of haemoglobin. In pernicious anaemia the bone marrow contains large amounts of protoporphyrin but there is uncertainty concerning its presence in megaloblasts. In diseases characterized by marked increases of uroporphyrin and coproporphyrin there has never been found any abnormality of the protoporphyrin metabolism. Such diseases are known as porphyria if they are due to inborn errors of metabolism or as porphyrinuric if they are secondary to other diseases. Congenital porphyria has the clinical features of photosensitivity, red teeth and bones and dark red or brown urine. Uroporphyrin is deposited in the skeleton and isomers of uroporphyrin and coproporphyrin are found in large amounts in the urine. Acute porphyria is associated with acute episodes of abdominal cramps, neurogenic paralyses and mental symptoms. The dark urine contains large amounts of uroporphyrin and coproporphyrin but no involvement of protoporphyrin has been found to occur in these diseases and there are present no marked anaemias such as might be attributed to an error in the formation of protoporphyrin. The porphyrinurias are diseases in which the excess of porphyrin is usually coproporphyrin, secondary to other diseases such as liver disease, pellagra, febrile conditions and diseases of the blood-forming organs. Protoporphyrin is involved in these only when anaemia exists.

Welcker, M. L. (1945) *New Engl. J. Med.*, 232, 11.

HAEMOTHORAX

See also B.E.M.P., Vol. VI, p. 156; and Cumulative Supplement, Key No. 604.

Treatment

Traumatic

Aspiration methods.—In New Guinea during the recent war, the treatment of traumatic haemothorax by e.g. thoracotomy, tube drainage or early aspiration with air replacement was precluded by the long distances from hospital and the lack of special equipment. Hayward describes the treatment of these cases by repeated aspirations. Although an uninfected haemothorax will absorb in time, the great fibrous pleural thickening which occurs often results in prolonged or permanent respiratory damage. It is true that early removal of fluid probably averts empyema formation in some cases but there is little danger of infection being introduced by aspiration or of haemorrhage being restarted. In New Guinea a sucking wound, or one from which blood was escaping, was sutured at once, often by stretcher-bearers in the

field At the advanced medical post treatment was usually expectant for 24 hours and included administration of routine prophylactic sulphonamides Tension pneumothorax must, however, be relieved by needling, if there was combined haemorrhage a blood transfusion was given and enough blood was aspirated to relieve dyspnoea In the average case, however, the first aspiration was not done until 48 hours after injury and thereafter the patient was transferred to hospital a task often requiring several days by land and air transport At staging posts on the way further aspirations or transfusions were performed as required and once in hospital aspiration was usually done every two or three days until the pleura was dry Tube drainage was sometimes necessary because of sepsis or other complication The aspirating needle must always be of adequate bore and length, namely No 14 British standard wire gauge and 4½ inches respectively Not more than one pint of fluid should be removed at each aspiration in order to prevent unduly high negative pressures Hayward points out that the clotting of blood in the pleural cavity may be minimal, with only a few fibrin threads, the blood remaining practically fluid through all the stages to the production of a large continuous coagulum This massive loculated clot cannot be aspirated and often thoracotomy is ultimately necessary to remove it The free fluid collecting above it can, however, be aspirated

Clotted haemothorax

Thomas and Cleland discuss the clinical and radiological features and treatment of clotted and infected haemothoraces Haemothorax, which may be associated with any of the various types of injury produced by blast or crushing, as well as with penetrating and perforating wounds is much the commonest complication in chest injuries In order to prevent pleural sepsis and eliminate it when it occurs, early and complete obliteration of the pleural space is the most important factor Earlier methods of treating clotted haemothoraces did not prevent incomplete or considerably delayed lung expansion, which often led to considerable deformity of the chest causing severe respiratory embarrassment in later life Some patients were left with severe and prolonged pleural infection which is largely responsible for base hospital mortality In a series of 750 chest injuries haemothoraces occurred in 526 cases (70 per cent) Infection was present in 30 per cent and clotting in 9 per cent of the haemothoraces Small clotted haemothoraces may be absorbed or organized leaving little residual disability, but in the larger ones there is much fibrous tissue formation with calcification or ossification later, causing a deformed and immobile or "frozen" chest Simple evacuation of the clot was at first tried, but in many cases the lung did not re expand, a residual pleural pocket remained which, in spite of repeated aspirations, was gradually obliterated by fibrous tissue, leaving the frozen chest Ultimately it was found that by decortication or removal of the fibrous tissue layer on the visceral pleura the lung was permitted to expand and fill the pleural cavity, the expansion being helped and hastened by suction drainage This gave considerably better results in a limited number of cases of haemothoraces than did any other method formerly used Decortication and suction drainage also gave good results in a small series of drained and undrained empyemas ensuing after haemothoraces

Hayward, J I (1945) *Aust NZ J Surg* 14, 157

Thomas, C P, and Cleland, W P (1945) *Lancet*, 1, 327

HAND, DISEASES AND DEFORMITIES

See also B E M P, Vol VI, p 171, and Cumulative Supplement Key Nos 613-617

Deformities

Acquired

Effects of immobilization—Girdwood discusses the disastrous effects of immobilization on the hand and its functions Substantial deformities may be caused by immobilization due to continuous relaxation of ligaments and reduction of the mechanical efficiency of the gliding surfaces of the bones In a hand in which wrist drop has been allowed, extension of the metacarpophalangeal joints has not been overcome and finger movements have been neglected, a vicious circle of atrophy, deformity and fixation runs its course The muscles atrophy and the hand takes the position of a typical, fixed claw hand and cannot form a fist or a strong grip This catastrophe can be avoided with care and proper treatment of the hand injury, whether wound, fracture dislocation, burn or infection In order to prevent the bad effects of immobilization, (1) the wrist should be extended giving maximum power to the flexor tendons, (2) the metacarpophalangeal joints should be fully flexed, putting the collateral ligaments of these joints on maximum stretch and allowing the interossei to act with the greatest possible mechanical advantage, and (3) the fingers should be allowed to move freely, keeping the interphalangeal joints from becoming fixed This position of the hand is 'the position of function', and a cycle of recovery is set in motion In cases of inevitable ankylosis of a metacarpophalangeal joint, that finger should be amputated, or if amputation is refused depends on the degree of deformity present The treatment of fixed claw hand fixed in flexion or, in more severe cases, operation may be necessary

Injuries

Causes and types of injury

Effect of the use of pneumatic tools—Hunter, McLaughlin and Perry consider, through study of the cases of 286 workers, the clinical effects produced by the use of pneumatic tools The tools vary in weight from 3 to 30 lbs and the speed of the piston in the different types

ranges between 250 and 6,000 strokes per minute. A right-handed worker supports the tool in the left gloved hand and the right hand controls the trigger. Such workers suffer from vascular disturbances producing local anaemia in the fingers, the characteristic "white finger" or "dead hand". The condition becomes more pronounced in cold weather. The symptoms usually appear 2-5 years after beginning pneumatic tool work and may necessitate abandonment of such employment; the percentage of cases rises with the length of working history. The hardness of the material worked upon and the vibration rate of the pneumatic tool are important factors in aetiology. The vibration is more pronounced at the striking end which is supported usually with the left hand. In a few cases the circulatory disturbances have induced gangrene of the finger. The escape of compressed air cools the instrument and the lowered temperature contributes to the vascular changes. A vibration rate of 2,500 strokes per minute is considered the critical level for the onset of white finger. Various methods of prevention have been tried, and it is believed that reduction of the vibration frequency would probably be the most successful. Decalcification of the carpal bones seen in x-ray examination is probably the result of jarring and not of rhythmical vibration as the incidence is greater among men using heavy tools with lower vibration rates. In the series reported on the incidence of arthritis of elbow and wrist is low. Only one man showed Dupuytren's contraction of palmar aponeurosis. Another patient showed well marked ulnar paresis and 2 others slight muscular wasting and loss of sensation.

Chronic inflammatory and miscellaneous conditions

De Quervain's disease

Signs, symptoms and treatment.—Aitken emphasizes the importance of early diagnosis and treatment of stenosing tendovaginitis at the radial styloid process, known as de Quervain's disease—a condition frequently missed by the general practitioner and industrial medical officer. Improperly treated the condition leads to prolonged painful disability. It occurs chiefly in women and has therefore been encountered more frequently since the employment of women in industry has increased. It is rare in patients under 25 years of age. Onset is usually insidious and history of trauma is lacking although acute cases after single trauma are seen. The condition is due to thickening of the fibrous sheath covering the tendons and synovial sheaths of abductor pollicis longus and abductor pollicis brevis at their passage through the groove in the radial styloid. The divergence of the tendons leads to considerable tension on the fibrous sheath on extension and abduction of the thumb. If the thumb is flexed in the palm, the fingers firmly flexed over it and the hand then forced into ulnar flexion acute pain occurs in de Quervain's disease but not in scaphoid fracture. Treatment is by operation under local anaesthesia; adhesions between sheath and tendons are divided and the edges of the fibrous sheath are excised; the skin only is closed and a compression dressing is applied.

Aitken, A. P. (1945) *New Engl. J. Med.*, **232**, 105.

Girdwood, W. (1944) *S. Afr. med. J.*, **18**, 350.

Hunter, D., McLaughlin, A. I. G., and Perry, K. M. A. (1945) *Brit. J. industr. Med.*, **2**, 10.

HEADACHE

See also B.E.M.P., Vol. VI, p. 199.

Clinical examination

Importance of the ophthalmoscope

Butler, in an address on headache and migraine, states that attempts to relieve headache should primarily include a decision whether or not it is of organic or functional origin. The 2 important causes of the former are intracranial disease and nephritis with its related factors, high blood pressure, retinal disease and uraemia. Cerebral tumours, the cardinal symptoms of which are headache, vomiting, papilloedema and exaggerated reflexes, are not uncommon. Nowadays, even when they are malignant cerebral tumours can be successfully removed by a skilled surgeon if they are at an early stage. In all cases of headache the ophthalmoscope should be used, the field of vision investigated, the urine examined and the blood pressure taken. Anaemias and affections of the sinuses are also common causes of headache. Contrary to general opinion, ocular defects are not very common causes, although headache occurs at the onset of presbyopia and is cured by the use of glasses for reading. After organic, ocular and septic origins have been excluded migraine should be considered. The characteristic headache in migraine is one-sided and becomes worse; there is vomiting and sometimes manifest polyuria. Scintillating scotomas generally precede the headache, the characteristic form starting as a very small centrally seen circle with a gradually widening zigzag periphery, and in bright spectrum hues. They occur symmetrically in each eye and generally do not last for more than a few minutes. Hemianopsia is also a common symptom, and is due to dimming of the field of vision in both eyes. Slight or marked vertigo is often present. Tingling in one arm with numbness, or aphasia, may occur. The author has found that diplopia is not uncommon. This symptom, vertigo and aphasia have been known to come on too often when the subject is driving a car for them to be due to mere coincidence. The cause of migraine is not known, although it is thought by some to be due to allergy.

Butler, T. H. (1944) *Med. Pr.*, **212**, 150.

HEART DISEASES: CONGENITAL DISEASES

See also B E M P, Vol VI, p 206, and Cumulative Supplement, Key Nos 619-635

Classification of malformations and expectation of life

Cyanotic group

Cor triloculare bivaiculare—Mehta and Hewlett describe a case of cor triloculare bivaiculare occurring in a woman, aged 56 years. This is the highest age recorded for bilocular and trilocular hearts, with persistent truncus arteriosus. The patient gave a history of fits which occurred during her childhood. There had been two attacks of rheumatic fever with no involvement of the heart. She had always been cyanosed, and there was clubbing of the fingers. The heart sounds were variable. A patch of bronchial breathing was detected at the upper part of the chest on the right side. Death was due to congestive heart failure. Necropsy showed the presence of gross cardiac deformity, but there was no evidence of rheumatic endocarditis. The atrium was incompletely and unequally divided by a fibrous septum which ended in a crescentic margin. Only two pulmonary veins opened into the part representing the left atrium. Only one ventricle was present, the right ventricle being represented by a small diverticulum. No signs were found either of the interventricular septum or of the pulmonary artery. A single large vessel representing the aorta arose from the ventricle. The first branch of the aorta was the innominate artery, and the right common carotid artery arose at the origin of this branch. One branch of the innominate artery appeared to turn downwards and was probably the pulmonary artery. No lung lesion was discovered which might have served to explain the cause of the area of bronchial breathing detected during life.

Patent ductus arteriosus

Treatment

Indications for ligation—In cases in which a patent ductus arteriosus is complicated by a subacute bacterial endarteritis the effect produced on the infection by ligating the ductus is so dramatic that Tubbs considers the presence of such infection to be an urgent indication for operation. In the past such cases, with few exceptions, were fatal in from one month to two years after the supravention of infection, whereas of the 9 patients treated surgically 6 have remained well for from 15 months to over 4 years after operation. Under cyclopropane and oxygen anaesthesia the skin was incised over the second intercostal space from the midline in front to the anterior axillary line, the medial $\frac{1}{2}$ inch of the second and third costal cartilages was excised together with their perichondrium and the pleural cavity was opened through the second intercostal space. Full exposure of the region below the aortic arch was then obtained by the aid of a single rib spreader. Because of the possibility of aneurysmal dilatation and inflammatory changes in the wall of the ductus particular gentleness is required to avoid accidental haemorrhage when the posteromedial surface is being freed. The ligatures each comprising two strands of silk, are passed behind the ductus by means of a malleable, blunt-ended aneurysm needle and are tied one at each extremity of the ductus. The mediastinal pleura is left unsutured and the chest is closed in layers. The rationale of this operation is at present inexplicable but Tourouff's theory seems as yet, to be the most reasonable. It supposes that the cessation of the rapid stream through the ductus results in much diminished fragmentation of the infected clot and that the lung capillaries, now less dilated and fed by an arterial stream no longer raised in pressure and volume, are able to filter off the few emboli which are formed, since vegetations occur primarily in the pulmonary end of the ductus, it is, therefore, a natural sequence that embolic phenomena in the lungs should precede those in the systemic circulation.

Results of ligation—The characteristic murmur of patent ductus arteriosus was originally described by Gibson in 1898 and Gilchrist suggests that this almost pathognomonic sign should henceforth be termed the Gibson murmur. Other signs, in order of importance, consist of dilatation of the pulmonary artery, an increased pulse pressure at rest or after exercise, and a long harsh basal systolic murmur with an accentuated or reduplicated pulmonary second sound. The diagnosis of an infected ductus is confirmed when repeated x ray examinations show changing patterns in the heart and lungs. The condition of patent ductus arteriosus is about twice as common in females as it is in males, but the author describes a series of 28 cases in which 13 patients were males. Surgical ligation was performed in 50 per cent of these cases. Four deaths occurred. 2 patients dying from subacute bacterial endocarditis, latter 2 cases one death was due to haemorrhage after a second attempt to ligate the ductus. The fatal issue in the other case was attributed to a deep-seated mediastinal infection. All but one of the survivors showed clinical improvement. By far the most spectacular result was obtained in a cardiac cripple, a boy aged 13 years, who was fully restored to perfect health within 2 years of the operation. The extent of improvement was more obvious in the older patients, since their physical handicap was greater than that of the younger members of the group. During the postoperative period a basal systolic murmur was detected in 4 patients and, subsequently, the Gibson murmur returned. On the average the diastolic blood pressure ultimately became stabilized at a level 30 millimetres of mercury higher than before ligation. It is recommended that younger patients should be selected for surgical treatment when symptoms are minimal, in the hope that by ductal occlusion the child may grow and develop normally. The operative hazards are greater in older patients, but in the presence of an infected ductus ligation should be undertaken immediately at any age.

Gilchrist, A. R. (1945) *Brit. Heart J.*, 7, 1.

Mehta, J. B., and Hewlett, R. F. L. (1945) *Brit. Heart J.*, 7, 41.

Tubbs, O. S. (1944) *Brit. J. Surg.*, 32, 1.

HEART DISEASES: PERICARDIUM DISEASES

See also B.E.M.P., Vol. VI, p. 256.

Aetiology

Congenital lesions of the pericardium

Pericardial defects.—Congenital pericardial defects are among the most uncommon of reported cardiac anomalies. Sunderland and Wright-Smith describe 2 more cases, in one of which the defect was directly responsible for the death of the patient. In neither case was the condition diagnosed or suspected during life. The authors consider that a number of factors, acting either singly or in combination, are responsible for the defect. The pericardium normally stretches coincidentally with the enlargement of the heart but, should there be premature enlargement preceding closure of the pleuropericardial foramen, projection of the heart through the opening will occur. Such projection is especially likely to take place when the foramen is abnormally large. Delay in closure of a normal pleuropericardial foramen will lead to its subsequent enlargement as the pericardium stretches. The arrested development may be due to premature obliteration of the duct of Cuvier, direct obstruction by the enlarging heart or disturbance of the growth mechanism whereby the connexion between the pleural and the pericardial cavities is gradually reduced to a minute foramen. In both of the authors' cases the defect was on the left side, as is usual. In one case there was the associated defect of a patent ductus arteriosus and in the other four lobes were present in the right lung. Sunderland and Wright-Smith restate Southworth and Stevenson's conclusions that, in cases in which there is a common cavity on the left side, the condition during life may be suspected by unexplained displacement of the heart to the left associated with abnormal mobility and enlargement.

Sunderland, S., and Wright-Smith, R. J. (1944) *Brit. Heart J.*, 6, 167.

HEART DISEASES: ENDOCARDITIS, MALIGNANT

See also B.E.M.P., Vol. VI, p. 299; and Cumulative Supplement, Key Nos. 644–646.

Subacute bacterial endocarditis

Aetiology

Review of pathogenesis theories.—Willius² propounds the conflicting theories of pathogenesis of subacute bacterial endocarditis, summarizing them under seven headings. (1) Rheumatic endocarditis and subacute bacterial endocarditis are forms of the same disease. (2) On blood platelet thrombi on irregular valve surfaces, micro-organisms circulating in the blood stream may lodge and may proliferate. (3) Nodular mononuclear endocardial cell proliferation ensues on thrombotic deposits and precedes formation of morphologically detectable endocardial defects. (4) Active rheumatic vegetations are requisite for the development of subacute bacterial endocarditis. (5) The outflow surfaces of injured valves are subjected to increased contact with blood micro-organisms and toxic agents. (6) Platelet thrombi on valves and transient presence of bacteria and antibodies in the blood, aid in its sterilization and in the focalization of bacteria. (7) Subacute bacterial endocarditis commences during transient bacteraemia and instead of normal response to infection there occurs on the chronically diseased valves a deposit of fibrin and blood platelets which attracts micro-organisms. Subacute bacterial endocarditis, however, can be superimposed on heart valves and structures not previously injured by rheumatic fever; and organisms not known to cause rheumatic fever can produce subacute bacterial endocarditis. The points of general agreement which emerge from this welter of contradictory theories and arguments are: (1) that a valve previously damaged by rheumatic fever, syphilis or arteriosclerosis or a congenital cardiac defect, is a prerequisite for development of subacute bacterial endocarditis; (2) that transient bacteraemia may participate in the pathogenesis of the disease; (3) that the reticulo-endothelial system, through the medium of hyperimmunity, plays a prominent part in the destruction of bacteria and in their focalization on the valves.

Bacteriology and morbid anatomy

Nature of the bacteria.—According to Willius¹, the bacteria which cause subacute endocarditis are usually of low virulence and are constantly being discharged into the blood stream. *Streptococcus viridans* is found in the blood and in heart valve vegetation in the great majority of cases. This micro-organism is characterized by the formation of green discoloration around the colonies on blood agar. A number of species of this group are causal agents of the disease. *Corynebacterium diphtheriae mitis* occurs, and is recoverable from the throat. Others, more rare, are *Streptococcus faecalis* and *Streptococcus liquefaciens*, both of which are found in the intestine, and *Streptococcus salivarius* which occurs in peri-apical dental foci and in the upper respiratory tract. *Staphylococcus aureus*, usually a cause of acute endocarditis, is sometimes found in the subacute condition; rarely, *Streptococcus pyogenes* plays a similar part. Gonococci usually produce a fulminating type, although occasionally the milder form, of the disease; meningococci may have a similar effect. Pneumococci rarely produce subacute endocarditis, but there have been numerous cases in which *Haemophilus influenzae* was the causal micro-organism. The influenzal group may cause endocarditis in

all grades of severity, *Haemophilus influenzae* being the most virulent. The brucella group of organisms may also cause the disease in all its forms. Mixed infections made up of multiple organisms, sometimes varying greatly in origin, have also been demonstrated as causal agents. Observations have indicated a general tendency for micro-organisms to increase as the disease progresses, but this increase is not constant and the number present at any time is no criterion of prognosis.

Effects of bacterial emboli—In an analysis of the various pathological changes resulting from the effects of subacute bacterial endocarditis, Willius* points out that for the development of the condition a previously damaged valve or a congenital cardiac defect is a prerequisite. At these sites there occur vegetations composed of irregular masses of fibrin, cellular blood elements and platelets enclosing micro organisms. The vegetations may also involve, from direct extension or by contact, the chordae tendineae and the mural endocardium of the left atrium and ventricle. Dissemination of bacterial emboli leads to the following lesions: (1) Pulmonary emboli, which occasionally are the cause of an erroneous diagnosis of pneumonia. (2) Minute emboli may involve the skin, mucous membranes and retinae. (3) Splenic infarcts are common, leading usually to moderate splenic enlargement, but perisplenitis may cause fixation of the organ and prevent diagnosis of enlargement by palpation. (4) The kidneys may suffer not only gross infarction but also the characteristic embolic form of glomerulonephritis. (5) Mycotic or infective aneurysms, usually small and involving more than one artery and other vascular structures, occur, but are rarely diagnosed during life. They may progress to rupture and fatal haemorrhage but not usually for several weeks or months. (6) Pericarditis rarely results from subacute bacterial endocarditis but has been reported in a case of spread of infection from a mycotic aneurysm of the aortic sinus. (7) Recent studies reveal frequent occurrence of myocardial lesions consisting of minute emboli, infarcts, abscesses, diffuse inflammation, Aschoff nodules and perivascular fibrosis. (8) Central nervous system involvement, the signs and symptoms of which may dominate the clinical picture, is fairly common in the course of subacute bacterial endocarditis.

Clinical picture

Main symptoms and signs—The haematology, signs and symptoms of subacute bacterial endocarditis are described by Willius*. Hypochromic anaemia—which increases as the disease advances—leucocytosis, leucopenia or a normal leucocyte count occurs, the blood platelet count is usually normal. There may be marked increase of monocytes, large phagocytic cells and syncytial masses of endothelial cells are inconstantly present. Symptoms are very variable and at the start are inconclusive, they are those common to the early stages of many infections and include general malaise, exhaustion, headache, pyrexia, chills, pains in joints, anorexia and nausea. When these symptoms appear in a patient with valvular disease, especially after dental extractions or tonsillitis, they should excite suspicion of subacute bacterial endocarditis. Later there will be loss of weight and strength, pain due to emboli, pleural type of pain, cough and dyspnoea. Visceral pain, due to gross infarction, may be the first important symptom and has led to suspicion of surgical abdominal conditions with consequent exploration. Pyrexia is often septic in type, for weeks or months it may not exceed 101° F. or it may remain normal for several days or weeks. There may be recurrent rigors followed by sudden temporary rises of temperature and sweats. Later there may be signs of congestive failure. Neurological manifestations may simulate anterior poliomyelitis, sciatica, polyneuritis, Schilder's disease, encephalitis lethargica, cerebral haemorrhage, syphilis or cerebral tumour. There may be symptoms referable to the respiratory system and recurrent pulmonary infarcts may be erroneously diagnosed as pneumonia.

Treatment

Chemotherapy—Willius* comments on the management and treatment of subacute bacterial endocarditis. There is no specific treatment, but 'occasional cures are forthcoming by the use of the sulphonamide compounds', and their trial alone or in conjunction with other agents, is justified. Failure of chemotherapy occurs if the drugs do not reach and destroy the organisms present in the cardiac vegetations. Sulphonamides combined with heparin or Dicoumarol have proved to be disappointing, and use of the latter agents is in any case hazardous. Hyperthermia alone or employed in combination with sulphonamides has failed. Sulphamerazine, the monomethyl derivative of sulphadiazine, is the newest sulphonamide. It is more rapidly and completely absorbed from the gastro intestinal tract and more slowly excreted in the urine than is sulphadiazine. Acetylsulphamerazine is twice as soluble in water as is that do other sulphonamides, and needs less frequent administration. Toxic effects must be avoided as far as is possible by daily administration in divided doses of 15 grammes of sodium bicarbonate and at least 3,000 cubic centimetres of water, unless otherwise contra indicated, so that a urinary output of at least 1,400 cubic centimetres is maintained. Since transient bacteraemia occurs after dental extraction or tonsillectomy, the author advocates administration before and after these operations of sulphonamides to victims of valvular defects or of congenital cardiac defects. Willius quotes Touroff's report on 12 operations for ligation of patent ductus arteriosus in presence of subacute bacterial endocarditis, there were 7 recoveries, 3 failures and 2 surgical deaths. Penicillin treatment has proved to be disappointing although its use, in 7 cases only, combined with heparin has appeared to be encouraging.

Penicillin—In a chronic disease such as subacute bacterial endocarditis, in which the in-

fection may remain latent for considerable periods of time, a long surveillance is subsequently necessary before assessing the results of any particular form of treatment. Dawson and Hunter consider that their experience with penicillin in this disease justifies the use of the drug when the infecting organism is a streptococcus sensitive to penicillin. They report on successful treatment in 15 of 20 patients. In 2 out of the remaining 5 the infection was controlled so long as penicillin was administered, but a relapse occurred with discontinuation of the therapy. The other 3 patients died, in each instance from cerebral embolus, but the infection was apparently still present. With the exception of these 3 patients—2 of whom were left with a residual hemiplegic and one with coronary occlusion—all the patients showing apparent recovery after periods of observation varying from months to 2 years, had returned to work. The value of heparin as an adjuvant to penicillin therapy is difficult to assess. Since major embolic phenomena are a serious complication the theoretical use of an anticoagulant seems to be justified, especially by the subcutaneous method described by Loewe. The amounts of heparin needed to maintain the coagulation time between 30 and 60 minutes varied greatly between patients. In one patient there developed a cerebral embolus at a time when his blood was adequately heparinized. The authors believe that the response to penicillin treatment alone is as favourable as when it is given in combination with heparin. Comparative studies showed that higher blood levels were usually obtained by continuous intramuscular drip than were obtained in those patients receiving penicillin by continuous intravenous drip. Moreover, the intramuscular drip is better tolerated and the technique is simpler.

Penicillin and heparin.—Loewe relates the effect of penicillin and heparin treatment in 54 cases of subacute bacterial endocarditis. He reviews previous treatment with heparin as an anticoagulant and chemotherapeutic drugs as anti-infective agents. The disease with few exceptions is of streptococcal origin arising from focal infections of teeth, tonsils, sinuses and the upper respiratory tract, a predisposing factor being the presence of valvular defects. It is recognized that even the severer forms of the disease may progress to spontaneous recovery and also that there may exist a milder and bacteria-free stage of the disease. Fibrin and blood elements are deposited on the valves, forming vegetations which protect the underlying bacteria from contact with anti-infective agents circulating in the blood. It is necessary to clear away these vegetations before anti-infective agents can be effective. Experimental study and necropsy observations indicated that heparin has an erosive action on endocardial vegetations. Because there is risk when it is given intravenously, heparin is administered by subcutaneous deposition and so is liberated more slowly with more equable absorption. The effect of heparin when used in association with the sulphonamides was just sufficient to be encouraging when penicillin became available as the anti-infective agent. The sensitivity of the infecting organism to penicillin was ascertained and on this basis the daily dosage of penicillin was calculated; it varies from 40,000 to 1,000,000 Oxford units. A 2-week course of treatment was found to be adequate for early endocardial lesions. When supplies of penicillin become more plentiful, the minimum course should be 5 weeks. Bigger dosage and more prolonged treatment are required for those whose condition shows bacterial activity. The best clinical results are obtained when the blood serum level of penicillin is 5–10 times that of the sensitivity figure. Of the author's 54 cases, 14 were recorded as failures and 40 patients were considered to be satisfactorily improved; 3 of them died later from other causes.

Acute bacterial endocarditis

Bacteriology and morbid anatomy

Differences in blood samples.—Beeson, Brannon and Warren state that the number of bacteria in the peripheral blood of a patient with bacterial endocarditis is usually small, despite the fact that organisms have free access to the circulating blood. This suggests that some mechanism is constantly at work to remove bacteria from the blood. In order to ascertain the nature of the process cultures were made from the blood of 6 patients with bacterial endocarditis. Blood was obtained not only from the peripheral arteries and veins but also from the right atrium, the venae cavae, the hepatic vein and the renal vein. Serial samples were taken and comparisons were made by counting the number of colonies derived from 1 cubic centimetre of blood. The counts were highest in arterial blood, and a remarkably constant level was maintained from minute to minute. The level was almost as high, however, in the blood from the antecubital veins. Therefore in clinical practice there is no advantage in taking samples from an artery rather than from an antecubital vein. A considerable portion of the bacterial content of the blood was found to disappear during one circuit of the body. This was proved by the fact that mixed venous blood in the right atrium usually had a colony count only a half to two-thirds as high as the corresponding arterial level. The investigations indicate that new supplies of bacteria are constantly being added to the blood at an even rate. Some bacteria appear to be removed in the liver, since comparatively small quantities of bacteria were obtained from the hepatic veins. The kidneys do not appear to remove many organisms since the renal veins contained many colonies. Nevertheless, other veins draining deep tissues, such as the femoral vein, contained blood with relatively few organisms.

Beeson, P. B., Brannon, E. S., and Warren, J. V. (1945) *J. exp. Med.*, 81, 9.

Dawson, M. H., and Hunter, T. H. (1945) *J. Amer. med. Ass.*, 127, 129.

Loewe, L. (1945) *Canad. med. Ass. J.*, 52, 1.

- Willius, F A (1944)¹ *Proc Mayo Clin*, 19, 380
 — (1944)² *Proc Mayo Clin*, 19, 431
 — (1944)³ *Proc Mayo Clin*, 19, 497
 — (1944)⁴ *Proc Mayo Clin*, 19, 521
 — (1945)⁵ *Proc Mayo Clin*, 20, 13

HEART DISEASES: MITRAL VALVE DISEASES

See also B E M P, Vol VI, p 309, and Cumulative Supplement, Key Nos 647-651

Mitral stenosis

Morbid anatomy

Circulatory changes in the bronchi—Ferguson, Kobilak and Deitrick describe a method for injecting the bronchial veins. The injections were made into the pulmonary veins with material consisting of a mixture of white lead, cinnabar, sucrose, gelatin and water. It was found that the bronchial veins became outlined as orange coloured lines on the mucosa of the smaller and medium sized bronchi. Few vessels were visible in the larger bronchi. Microscopic section showed that some vessels were situated between the cartilaginous plates of the bronchi. These vessels appeared to connect the bronchial and pulmonary veins. At necropsies on patients who had died of cardiac failure due to hypertension it was demonstrated that the bronchial veins of the larger bronchi were slightly dilated. Age and hypertension did not affect the normal capacity of the bronchial veins unless chronic congestive heart failure had occurred. There were 11 necropsies on patients who had died of mitral stenosis of rheumatic origin. Six showed evidence of dilated venous channels. In 4 the secondary and tertiary bronchi contained innumerable wide venous channels running parallel to the lumen. It is believed that the presence of mitral stenosis hinders the flow through the pulmonary veins to the left atrium. The pressure in the pulmonary veins rises above that in the right atrium and the blood flow through the anastomosis is reversed. The blood passes from the pulmonary circulation into the bronchial veins and back to the right side of the heart, along the course of the azygos, hemi azygos and intercostal veins. As a result of the establishment of this collateral flow varices appear in the submucosal bronchial veins of the larger bronchi. Haemoptysis often occurs in mitral stenosis and in the absence of pulmonary oedema or infarction, the haemorrhage is probably caused by rupture or ulceration of the engorged bronchial veins.

Clinical picture

Incidence of hypertension—Horns discusses the incidence of hypertension in patients with mitral stenosis. The group consisted of 43 males and 101 females, and the ages ranged from 20 to 87 years. Cases in which there were lesions of the aortic valve were excluded. A comparison was made between the group and a series of 288 cases taken at random from the records of the out patient clinic of the University Hospital, Minneapolis. The groups were matched for age and sex. The criterion of hypertension was constituted by readings exceeding the systolic and diastolic blood pressures of 150 and 90 millimetres of mercury, respectively. Terminal falls of blood pressure were not included in the records. It appears, however, that a fall of blood pressure does not usually accompany mitral stenosis complicated by heart failure. In patients over the age of 45 years the incidence of hypertension was 30 per cent of those with mitral stenosis and 31 per cent of the cases in the other group. In the former series the systolic and diastolic blood pressures yielded an average of 144.4 ± 3.02 and 86.2 ± 1.75 millimetres of mercury. The corresponding measurements in the second group were 148.2 ± 2.34 and 88.9 ± 1.09 millimetres of mercury. These findings are in close agreement. There is thus no evidence that hypertension occurs more often in those with mitral stenosis than in any other type of patient. Moreover, a study of the average age at death does not indicate that the presence of hypertension confers an increased expectation of life upon a person with mitral disease.

Mitral regurgitation

Diagnosis

Rupture of the chordae tendineae—Bailey and Hickam describe in detail the clinical signs, symptoms and pathology of 7 cases of rupture of the mitral chordae tendineae in which there was no evidence of underlying bacterial endocarditis. At necropsy all cases showed evidence that chronic damage to the mitral valve had preceded rupture of the chordae tendineae. In 2 cases the lesions were the result of rheumatic heart disease but in the others the damage, although suggestive, was not pathognomonic. No difference in the frequency of rupture of the chordae to either cusp was found and generally more than one chorda tendinea was ruptured close to the papillary muscle, the latter showed atrophy if all its chordae were ruptured, but hypertrophy if some remained intact. Mitral regurgitation followed rupture, tendineae may rupture after chest trauma or sudden exertion but in the quoted series there was no evidence to suggest that such trauma may be the primary cause of rupture. After rupture of the mitral chordae signs and symptoms of congestive cardiac failure appear, and the condition may have an abrupt or insidious course with remissions, years may elapse before failure occurs. In all patients in the authors' series there developed a loud presystolic murmur, usually with a thrill, and maximal at the apex of the heart. The sudden onset of such a murmur in a middle aged person is suggestive of rupture of the chordae tendineae. An apical diastolic murmur and atrial fibrillation may also be present. X ray examination

of 4 cases showed an enlarged heart and in one case a systolic pulsation of the left auricle, a sign of marked mitral regurgitation which may be pathognomonic of the disease. The differential diagnosis lies between bacterial endocarditis, rupture of the valves or a papillary muscle and spontaneous perforation of an infarcted ventricular septum.

Diagnosis

Electrocardiographic changes

White, Parker and Master attempt to evaluate the electrocardiographic changes commonly recognized in mitral disease. Standardized electrocardiograms were obtained from 100 control subjects, 100 subjects with functional systolic murmurs, 43 subjects with mitral insufficiency and 22 subjects with mitral stenosis. On arithmetical probability graph paper the authors tabulated the cumulative percentages of the following data as found in the various clinical groups: heights of the P waves in leads I, II and III, width of the widest P wave in any lead, and degree of notching of the P waves, deep notching being recorded when the notch returned halfway or more to the base lines. The angle of the electrical axis was also determined but proved to be diagnostically valueless. Subjects with functional systolic murmurs showed no difference in their electrocardiographic patterns from control subjects of similar age. Changes occurred in the P waves of some subjects with mitral insufficiency, but not often enough to be of diagnostic importance. The authors suggest that P waves 3 millimetres or more in height in lead II, 0.12 second or more in width in any lead or deeply notched in 2 or more leads be considered to be abnormal. One or more of these changes occurred in 62 per cent of their patients with mitral stenosis as compared with 4 per cent of controls. Tall P waves appeared usually in leads II or III. These electrocardiographic changes, the authors consider, are statistically significant and may be accepted as of corroborative but not of specific diagnostic value.

Bailey, O. T., and Hickam, J. B. (1944) *Amer. Heart J.*, 28, 578.

Ferguson, F. C., Kobilak, R. E., and Deitrick, J. E. (1944) *Amer. Heart J.*, 28, 445.

Horns, H. L. (1944) *Amer. Heart J.*, 28, 435.

White, B. V., Parker, R. C., Jun., and Master, A. M. (1944) *Arch. intern. Med.*, 74, 94.

HEART DISEASES: AORTIC VALVE DISEASES

See also B.E.M.P., Vol. VI, p. 329.

Clinical picture

Aortic regurgitation

Investigation of apical cardiac sounds.—A phonocardiographic study was made by Luisada of 27 patients with syphilitic aortic regurgitation in order to investigate the cardiac sounds at the apex. Patients with rheumatic heart disease were not included. The records were taken with a Stetho-cardiette (Sanborn) and the tracings recorded were as follows. (1) A routine electrocardiogram, coupled with a routine phonocardiogram. (2) Lead I of the electrocardiogram and the apex phonocardiogram by using the stethoscopic microphone. (3) The same record but using a logarithmic microphone. (4) Apex sounds and apex beat. (5) Various other records, such as the phlebogram, arteriogram and pneumocardiogram. Different auscultatory phenomena during diastole were found, which were probably due to different mechanisms. In the first group of cases some showed during presystole a very ample and slow vibration, identical with the loud atrial sound which causes presystolic gallop rhythm. In other cases a loud third sound of the heart occurred, succeeded by an atrial sound. These two sounds during diastole may give the impression of a diastolic rumble. In the second group the patients were thought clinically to have a presystolic murmur; in reality this was found to be a distorted first sound of a "crescendo" type occurring in systole. That such was the case was shown by comparison of a stethoscopic microphone tracing with the simultaneously recorded electrocardiogram. In cases of the third group a split first sound occurred, due either to unusual loudness of the mitral and aortic valve sounds or to increased intensity of the vascular component of the first sound, that is, either a separation of the two valvular sounds composing the first sound, or a separation of the valve sounds from the vascular component. It is doubtful whether any of the cases showed an Austin Flint murmur, described by Austin Flint as a presystolic blubbery murmur heard at the apex in cases of aortic regurgitation due to syphilitic and arteriosclerotic heart disease.

Luisada, A. A. (1944) *Amer. Heart J.*, 28, 156.

HEART DISEASES: HEART FAILURE

See also B.E.M.P., Vol. VI, p. 368; and Cumulative Supplement, Key No. 659.

Treatment

Drugs
Effect of Esidrone.—The toxic effects of the mercurial diuretics have been recognized since their use in the treatment of heart failure became popular. Many of the earlier contra-indications such as albuminuria, raised blood pressure and increase of non-protein nitrogen in the blood, have been modified by increasing experience in dealing with the drugs. The important renal contra-indications are acute or chronic glomerulonephritis and malignant nephrosclerosis; diminished specific gravity of the urine must be regarded with suspicion.

- Willius F A (1944)¹ *Proc Mayo Clin*, 19, 380
 — (1944)² *Proc Mayo Clin*, 19, 431
 — (1944)³ *Proc Mayo Clin*, 19, 497
 — (1944)⁴ *Proc Mayo Clin*, 19, 521
 — (1945)⁵ *Proc Mayo Clin*, 20, 13

HEART DISEASES: MITRAL VALVE DISEASES

See also B E M P, Vol VI, p 309, and Cumulative Supplement, Key Nos 647-651

Mitral stenosis

Morbid anatomy

Circulatory changes in the bronchi—Ferguson, Kobilak and Deitrick describe a method for injecting the bronchial veins. The injections were made into the pulmonary veins with material consisting of a mixture of white lead, cinnabar, sucrose, gelatin and water. It was found that the bronchial veins became outlined as orange coloured lines on the mucosa of the smaller and medium sized bronchi. Few vessels were visible in the larger bronchi. Microscopic section showed that some vessels were situated between the cartilaginous plates of the bronchi. These vessels appeared to connect the bronchial and pulmonary veins. At necropsies on patients who had died of cardiac failure due to hypertension it was demonstrated that the bronchial veins of the larger bronchi were slightly dilated. Age and hypertension did not affect the normal capacity of the bronchial veins unless chronic congestive heart failure had occurred. There were 11 necropsies on patients who had died of mitral stenosis of rheumatic origin. Six showed evidence of dilated venous channels. In 4 the secondary and tertiary bronchi contained innumerable wide venous channels running parallel to the lumen. It is believed that the presence of mitral stenosis hinders the flow through the pulmonary veins to the left atrium. The pressure in the pulmonary veins rises above that in the right atrium and the blood flow through the anastomosis is reversed. The blood passes from the pulmonary circulation into the bronchial veins and back to the right side of the heart, along the course of the azygos, hemi azygos and intercostal veins. As a result of the establishment of this collateral flow varices appear in the submucosal bronchial veins of the larger bronchi. Haemoptysis often occurs in mitral stenosis and, in the absence of pulmonary oedema or infarction the haemorrhage is probably caused by rupture or ulceration of the engorged bronchial veins.

Clinical picture

Incidence of hypertension—Horns discusses the incidence of hypertension in patients with mitral stenosis. The group consisted of 43 males and 101 females, and the ages ranged from 20 to 87 years. Cases in which there were lesions of the aortic valve were excluded. A comparison was made between the group and a series of 288 cases taken at random from the records of the out patient clinic of the University Hospital, Minneapolis. The groups were matched for age and sex. The criterion of hypertension was constituted by readings exceeding the systolic and diastolic blood pressures of 150 and 90 millimetres of mercury, respectively. Terminal falls of blood pressure were not included in the records. It appears, however, that a fall of blood pressure does not usually accompany mitral stenosis complicated by heart failure. In patients over the age of 45 years the incidence of hypertension was 30 per cent of those with mitral stenosis and 31 per cent of the cases in the other group. In the former series the systolic and diastolic blood pressures yielded an average of 144.4 ± 3.02 and 86.2 ± 1.75 millimetres of mercury. The corresponding measurements in the second group were 148.2 ± 2.34 and 88.9 ± 1.09 millimetres of mercury. These findings are in close agreement. There is thus no evidence that hypertension occurs more often in those with mitral stenosis than in any other type of patient. Moreover, a study of the average age at death upon a person with mitral disease.

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Diagnosis

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cardium determine the diagnosis. Coronary artery disease may give symptoms suggestive of a gastric origin. The onset of cardiac infarction may closely resemble the symptoms of an acute abdomen or of food poisoning. In patients with subacute bacterial endocarditis, auricular fibrillation or mitral disease emboli from the left heart may lodge in the mesenteric arteries, giving rise to symptoms of acute abdominal disease. Patients with paroxysmal tachycardia or extrasystoles may complain of flatulence and upper abdominal distress. In mitral stenosis an enlarged left atrium may exert pressure on the oesophagus, causing dysphagia in addition to other dyspeptic symptoms. Prolonged treatment with digitalis may be followed by gastric symptoms. In congestive heart failure digitalis preparations such as Digoxin and Cedilanid may be better tolerated. Theobromine and other purine diuretics may also cause gastric irritation.

Complications

Pneumonia supervening on heart disease

Treatment by potassium bicarbonate.—Ohnysty and Wolfson stress the value of potassium bicarbonate in rendering the urine alkaline as an adjunct to sulphadiazine therapy in cases of pneumonia complicating cardiac impairment. Sodium bicarbonate is more often used but this salt causes sodium retention which may precipitate cardiac oedema. In order to establish the advantages of employing the potassium salt, the authors treated a group of 16 patients with severe cardiac impairment and pneumonia. The criteria for including cases in the investigation were demonstration of the presence of pneumonia, survival for at least 72 hours after admission to hospital and cardiac decompensation classified as grade III or IV according to the specifications of the American Heart Association. Patients with renal or suprarenal insufficiency were excluded in view of possible occurrence of toxic effects due to potassium. All patients received an initial dose of 4 grammes of sulphadiazine and a subsequent dosage of 1 gramme every 4 hours. Nine patients were given a preliminary dose of 8 grammes of potassium bicarbonate and then 2 grammes every 4 hours. A similar dosage of sodium bicarbonate was administered in the remaining cases. Fluids were given freely and measurements were made of the daily intake and output. It was found that the patients who were treated with potassium bicarbonate excreted an average of about 250 cubic centimetres of fluid daily in excess of the output of those given the sodium salt. No signs of intolerance to potassium were noted and the excretion of retained water and sodium facilitated the re-establishment of cardiac compensation.

Ohnysty, J., and Wolfson, W. Q. (1944) *New Engl. J. Med.*, 231, 381.

Scott, J. W. (1945) *Canad. med. Ass. J.*, 52, 128.

HEPATO-LENTICULAR DEGENERATION

See also B.E.M.P., Vol. VI, p. 443.

Clinical picture

Diagnostic and prognostic features

Glazebrook describes 2 cases of Wilson's disease which exhibit the syndrome of hepatolenticular degeneration. Its aetiology is obscure. Degenerative changes in the brain are probably secondary to disease of the liver. The first case described is that of a male, 17 years of age, who was admitted to an Edinburgh hospital suffering from torsion spasms with a history of "encephalitis" at the age of 10. There was no history of jaundice. He presented a striking picture of rigidity, and tolerance tests with galactose and laevulose proved that there was hepatic insufficiency. The patient's father and probably 2 brothers of the father were affected with lenticular disease. Wilson's disease developed in the second case, also a boy of 17, 3 years after an attack of jaundice with hepatomegaly. His clinical condition was typical of the disease. His blood copper was found to be 0.30 milligram per 100 cubic centimetres. At necropsy a marked excess of copper was found in the liver and in the basal ganglia. Recent studies have shown that lenticular degeneration can result from liver damage due to various causes, such as alcoholism, syphilis and diabetes. In domestic animals nervous symptoms also appear after acquired hepatic cirrhosis, with degenerative lesions in the cortex and caudate nuclei similar to those of hepatolenticular degeneration. In Wilson's disease large quantities of copper accumulate in the tissues and these accumulations powerfully inhibit enzymic activity and interfere in some unknown manner with the rich blood supply of the basal ganglia, so causing a focal necrotic lesion. A raised blood copper content may therefore be of diagnostic and prognostic value.

Glazebrook, A. J. (1945) *Edinb. med. J.*, 52, 83.

HERNIA

See also B.E.M.P., Vol. VI, p. 470; and Cumulative Supplement, Key Nos. 672-687.

External abdominal hernia

Treatment

Fascial transplantation.—Singleton and Stehouwer advocate using the patch type of free fascial transplant for treatment of suitable difficult or large hernias but emphasize the importance of careful technique. Failure is often due to disregard of the principles of physiological stress and strain. The transplant must be cut parallel to its fibres and so placed in its bed that its fibres run parallel to those of the inguinal ligament or of the rectus abdominis sheath, or shearing and tensile stress may cause disintegration of the transplant. To ensure adequate

Pines, Sanabria and Arriens however, point out that new toxic effects have been described, some of them connected with the mercurials themselves and some with the resulting diuresis. Since several of the reactions cannot be foreseen and are rapidly fatal, their recognition is of considerable importance. These reactions include circulatory disturbances associated with dehydration, haemoconcentration, chloride depletion and derangement in water balance. Various studies have indicated that oedema fluid of digitalized patients, when it finds its way rapidly into the blood stream in mercurial diuresis, may effect redigitalization with toxic symptoms. There may occur also spontaneous tetany, pulmonary oedema and hypersensitivity reactions. The effects of mercurials on cardiac muscle have been less understood and the authors, after experiments with Esidrone on dogs, conclude that mercurial diuretics in certain doses are general depressants for the whole cardiac muscle, producing conduction disturbances, ventricular fibrillation and death. The addition of small quantities of magnesium sulphate (0.5 cubic centimetre of a 20 per cent solution) prevents fibrillation and death, it does not however influence—except possibly adversely—the conduction disturbances produced by lethal mercurial doses. The magnesium sulphate is not harmful, increases the diuretic response and mixes with the mercurials without forming any precipitate. Pines, Sanabria and Arriens recommend therefore that small quantities of magnesium sulphate should be incorporated into the mercurial diuretics in order to prevent fatal reactions resulting from their intravenous administration.

Morphine in congestive heart failure—Cookson lauds morphine for treatment of congestive heart failure except when Cheyne Stokes breathing is present or when the failure is associated with chronic lung disease. For acute pulmonary congestion he advocates neither atropine nor adrenaline nor nikethamide but administers morphine at the earliest possible moment in a $\frac{1}{4}$ grain dose or, if a severe attack has lasted for more than half an hour, a $\frac{1}{2}$ -grain dose. If there is no relief after 20 minutes he gives another $\frac{1}{4}$ -grain dose and this is repeated every 20 minutes until the attack subsides. Cookson says "as much as $\frac{1}{2}$ grains of morphine may be needed for a severe neglected attack". If even this quantity fails, venesection is indicated. The author suggests that by depressing the respiratory centre morphine breaks the vicious circle of pulmonary engorgement and consequent respiratory stimulation. Chronic pulmonary and systemic congestion he treats with rest, restriction of fluid and salt and administration of morphine, diuretics and digitalis, emphasizing that "neither high blood pressure nor aortic incompetence calls for any caution in the use of digitalis though this teaching dies hard", and that "digitalis is indicated in failure, whether or not the heart rhythm is regular, fast or slow, and even a rate of 30 per minute, due to heart block, would be no contra indication if failure were present".

General

Is rest in bed justifiable?—Levine reviews the accepted treatment by rest in bed of severe cardiac disease. He admits the fundamental necessity of this principle in treatment, but points out that in certain conditions it is harmful. When the working energy of the two sides of the heart is not balanced, congestion will occur either in the venous return or in the pulmonary circuit. Oedema of the legs is not dangerous. Recumbency will tend to transfer this oedema to the chest, causing hydrothorax or pulmonary congestion with increase of breathlessness. A sitting up posture with the legs hanging down will relieve this distress. Patients themselves are aware of this, dread to lie in bed and prefer to sit in a chair. Prolonged recumbency in the case of these patients may also be harmful in that it predisposes to thrombophlebitis of the legs with the danger of pulmonary embolism. The commonness of this complication is only now being appreciated. These thrombi in the lower extremities are most likely to develop in obese cardiac patients because of abdominal pressure on the veins of the thigh and the pelvis. In order to prevent pulmonary embolism, ligation of the femoral vein is advisable as soon as the patient complains of pain which is usually in the calf on dorsiflexion of the foot. Patients with cardiac dyspnoea should rest on a bed made to slant downwards from head to foot by being raised on 9 inch wooden blocks. Patients with heart disease who are in bed should have their lower extremities exercised actively and with massage in order to lessen the risk of thrombophlebitis.

Cookson, H (1944) *Practitioner*, 153 155

Levine, S. A (1944) *J Amer med Ass*, 128 80

Pines, I., Sanabria A. and Arriens, R. T. H (1944) *Brit Heart J*, 6, 197

HEART DISEASES—GENERAL

Clinical picture

Gastro-intestinal symptoms and cardiovascular disease

Scott discusses the relationship between gastro intestinal symptoms and cardiovascular disease, believing that there is some truth in the statement that when an old man complains of gastric symptoms his cardiac condition should be investigated. Symptoms grouped together as dyspepsia are commonly encountered, yet a fair proportion of dyspeptics have no organic gastric disease. In congestive heart failure dyspeptic symptoms are prominent since they are caused by portal stasis initiating unpleasant sensations made worse after a meal and simulating cholecystitis. In a patient aged over 40 years a heart lesion may effectively mimic a diseased gallbladder. Chronic constrictive pericarditis is not easy to differentiate from portal cirrhosis. The engorgement of neck veins and x ray evidence of calcification of the peri-

cardium determine the diagnosis. Coronary artery disease may give symptoms suggestive of a gastric origin. The onset of cardiac infarction may closely resemble the symptoms of an acute abdomen or of food poisoning. In patients with subacute bacterial endocarditis, auricular fibrillation or mitral disease emboli from the left heart may lodge in the mesenteric arteries, giving rise to symptoms of acute abdominal disease. Patients with paroxysmal tachycardia or extrasystoles may complain of flatulence and upper abdominal distress. In mitral stenosis an enlarged left atrium may exert pressure on the oesophagus, causing dysphagia in addition to other dyspeptic symptoms. Prolonged treatment with digitalis may be followed by gastric symptoms. In congestive heart failure digitalis preparations such as Digoxin and Cedilanid may be better tolerated. Theobromine and other purine diuretics may also cause gastric irritation.

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External abdominal hernia

Treatment

Fascial transplantation.—Singleton and Stehouwer advocate using the patch type of free fascial transplant for treatment of suitable difficult or large hernias but emphasize the importance of careful technique. Failure is often due to disregard of the principles of physiological stress and strain. The transplant must be cut parallel to its fibres and so placed in its bed that its fibres run parallel to those of the inguinal ligament or of the rectus abdominis sheath, or shearing and tensile stress may cause disintegration of the transplant. To ensure adequate

lymph supply all loose areolar and fatty tissues must be removed from the graft before it is sutured into place. Sutures and ligaments, moreover, must be tight when the transplant is fixed to the surrounding tissue in order to ensure close contact and also, by traumatizing the muscle to produce the fibrin formation and consequent fibrosis upon which firm union depends. Owing to the rich blood supply of muscles tight ligatures do not cause necrosis. Since success depends upon the type and degree of union between the graft and the overlapping edges of the defect, the patch must be larger than the defect. In repairing direct hernia the corner of the fascial patch must be securely sutured and anchored to the pectineal (lacunar) part as well as to the shelving portion of the inguinal ligament.

General treatment of hernia—Brandon states that the main disadvantage of the Bassini operation is its inability to protect the internal ring against the formation of a new sac. Operations for large oblique and acquired herniae should, in his opinion, be designed to scrap the stretched and weakened internal ring entirely and construct a new one. He believes that there is no necessity for operations which require the introduction of large quantities of unabsorbable suture material or secondary operations on the thigh and sets out the stages of an operation which he considers to be quite as efficient as Schmieden's and which is easier and less traumatic. The steps of the standard operation are followed up to the point at which the cremaster has been incised and the contents of the cord exposed. After division of the internal oblique and transversus abdominis muscles, the sac is isolated, ligated at its neck and excised. The cut ends of the muscles are separated and the torn or stretched transversalis fascia is closed. The cut muscles are reconstituted around the cord which now emerges through a satisfactorily fitting aperture placed well out in a lateral position. The conjoined inguinal canal. Brandon advocates the standard operation for small congenital hernia with good muscles and the modified operation for longstanding congenital hernia in which the internal ring has become stretched but the muscles are still good. For a direct inguinal hernia the repair should aim at the construction of a strong posterior wall, since the hernia results from progressive atrophy of muscles and fasciae in the region of the canal. Here the silk lattice repair of the Ogilvie type fulfils its most useful function. Postoperative care is essential, but Brandon emphasizes that the fate of a hernia is sealed on the operation table.

Whole-skin grafts—In a preliminary report on the use of whole skin grafts in the treatment of hernia, Mair considers that much better results are given by this method than by the use of fascia or cutis graft repair. Experimental work on rabbits showed that 5 months after operation the whole skin graft had become firmly attached to its surroundings and closely resembled normal fascia, the degree of metaplasia being very striking. A similar result was found in a human subject in whom exploration happened to be possible 3 months after a whole skin graft had been used for a large direct hernia. In a series of 70 inguinal, 6 umbilical, 10 ventral, 1 epigastric and 1 femoral herniae a whole skin graft was used in repair with satisfactory immediate results, it is too early for recurrence figures to be given. The graft is formed of an ellipse of skin 2 inches long and approximately 1 inch at its broadest diameter, excised from the operation site with attached subcutaneous tissue. Whole-skin graft is advocated for use in large and difficult hernia cases and its general applicability to any type of hernia is emphasized. When correctly applied the graft affords protection to the entire inguinal canal and narrows the internal ring but care must be taken not to narrow it too much. The only postoperative complications in the series were 2 cases of mild sepsis which cleared up quickly, 1 case of scrotal haematoma and 2 cases of bronchitis. The operation takes less time to perform than does a fascial repair, and the finished immediate result appears to be stronger. After removal of the graft no difficulty was found in closing the skin wound.

Brandon, W. J. M. (1945) *Lancet*, 1, 167.

Mair, G. B. (1945) *Brit. J. Surg.*, 32, 381.

Singleton, A. O., and Stehouwer, O. W. (1945) *Surg. Gynec. Obstet.*, 80, 243.

HERPES

See also B. E. M. P., Vol. VI, p. 513, and Cumulative Supplement, Key Nos. 688 and 689.

Herpes zoster

Clinical picture

Ramsay Hunt syndrome—Shulack and Kibbe describe a case of herpes zoster auricularis with facial palsy and auditory symptoms, a combination of symptoms grouped as a syndrome by Ramsay Hunt in 1907. Herpes zoster, according to present knowledge, is considered to be probably due to a filtrable virus akin to that of varicella, which causes a localized inflammatory reaction in a spinal or cranial sensory ganglion with involvement of the corresponding dorsal root, posterior grey horn and adjacent meninges, and sometimes with the anterior horn as well. A 27-year-old soldier was admitted to the Station Hospital, Fort Benning, Georgia, complaining of vertigo, inability to close the right eye, pain in the right ear with diminished hearing, and occipital headache. He was found to have complete right facial paralysis, redness in the right concha with later a very tender vesicular eruption right hypsilateral to the ear. He was considered to be hysterical in origin—absent motor corneal reflex on the right side with retention of right consensual corneal reflex, and generalized tendon hyper-reflexia. The spinal fluid, otherwise normal, showed a pleocytosis (44 cells per cubic millimetre) at the height

of the disease; there was a recession of the pleocytosis (6 cells per cubic millimetre) on recovery. No other abnormalities were found after complete investigation of all systems. The patient was vaccinated with attenuated smallpox virus, with an immune reaction result. He was fed on a high calorie, high vitamin diet with 30 milligrams of thiamine chloride (aneurine hydrochloride) daily by the mouth. Radiant heat and massage was given later to the right facial muscles. Progress was uneventful and the patient returned to duty, 42 days after admission to hospital, with no subjective symptoms and with normal hearing and approximately 80 per cent recovery of the facial paralysis. The case shows neurological and spinal fluid evidence of a localized central nervous system inflammation as the probable basis of the syndrome.

Shulack, N. R., and Kibbe, M. H. (1945) *J. nerv. ment. Dis.*, **101**, 9.

HISTOPLASMOSIS

See also B.E.M.P., Vol. VI, p. 520.

Clinical picture

Physical signs

Fatality of the disease.—Parsons and Zarafonietis review 78 cases of histoplasmosis in man. Histoplasmosis is a fungus disease attacking the cells of the reticulo-endothelial system and was first described by Darling in 1905. It seems to be likely that its incidence has increased during recent years. It has a worldwide distribution and attacks both white and coloured races. Up to the age of 10 years the sex distribution is equal, but above that age males are more frequently attacked than are females. The higher incidence in males may be due to their occupations in adult life, which are different from those of females, but it has not been observed that the disease is confined to any particular occupation. No age group is immune from histoplasmosis. The infection manifests itself in many ways, the portal of entry is not yet certain, and it must be remembered that the fungus so far has not been found in its vegetative form in nature. Ulcerative lesions of the skin, mucous membranes, eye, ear, nose, mouth and pharynx and enlarged lymph glands can occur. If the lungs are involved the disease can coexist with pulmonary tuberculosis, which it closely resembles. The liver and spleen are often enlarged, the gastro-intestinal tract may be involved and 3 cases of vegetative endocarditis have been described. Moderate to severe anaemia is usually present with irregular fever, and wide variations occur in the total and differential leucocyte counts. The disease is almost certainly fatal, the majority of patients living less than one year from the onset of the illness. The diagnosis is not easy; the yeast-like form of *Histoplasma capsulatum* may be found in the leucocytes of a blood smear and also on examination of the sternal bone marrow. Examination of biopsy material has been so far the most successful way of detecting the disease. Positive diagnosis is certain when the organism is cultured and the mycelial form identified. Cultures grow slowly and should be kept for 3–4 weeks before being considered to be negative. Diagnosis by skin tests and animal inoculation have proved to be successful in some cases. The lesions produced may be confused with those of more common diseases such as tuberculosis, carcinoma and Hodgkin's disease, as well as with leukaemias and other blood dyscrasias. Histoplasmosis may cause suprarenal insufficiency in cases of extreme hypotension and may also closely resemble leishmanian infections. The treatment of the disease is still in the experimental stage. The authors suggest that a diamidine preparation and certain antimony preparations merit further trial.

Parsons, R. J., and Zarafonietis, C. J. D. (1945) *Arch. intern. Med.*, **75**, 1.

HODGKIN'S DISEASE

See also B.E.M.P., Vol. VI, p. 523; and Cumulative Supplement, Key No. 691.

Clinical picture

Lesions in various organs

Value of x-ray therapy.—Wolpaw, Higley and Hauser report the study of a series of 55 cases of Hodgkin's disease the diagnosis of which was confirmed by biopsy or necropsy. A typical case of the disease with enlargement of the peripheral glands is well known but the frequency of involvement of spleen, liver, lungs, pleura and bone is less well recognized. Of 55 cases 35 showed intrathoracic involvement. Fifteen cases are described in detail. Manifestations of Hodgkin's disease within the thorax are correlated with the anatomical distribution of lymphoid tissue, which is abundantly present in the mediastinum, lung parenchyma and pleura. The pathological process starting in one set of glands is very liable to spread to another. The mediastinal glands comprised 50 per cent of the authors' series, the hilar glands being those most commonly involved. With massive enlargement of these glands the patient will have an irritative cough and dyspnoea together with the usual signs and symptoms of Hodgkin's disease. Lung parenchyma was involved in 40 per cent of the series. These present great difficulty in x-ray diagnosis. The lung may be involved by direct infiltration from the mediastinum or by infiltration along the peribronchial and perivascular lymphatic vessels or by extension of the disease through the alveoli. Such cases showed all the signs and symptoms of pulmonary disease. Pleural involvement occurred often, with massive and persistent effusions. Effusion may occur independently of pleural involvement on account of pressure on the lymphatics by the enlarged hilar glands. The disease may originate in the sternum and ribs or spread into them from other sources. The disease may spread from other organs into the heart, with changes in its rhythm and configuration. X-ray

therapy proved to be of some value in many of these cases, the disease retrogressing and life being prolonged. Twenty three of the 35 cases were treated by irradiation and 17 showed a distinctly favourable response.

Skin

Dysvitaminosis and dermal atrophy—Glazebrook and Tomaszewski report a case of generalized ichthyosiform atrophy of the skin due to a disturbance of the metabolism of vitamin A. Other abnormalities included alopecia, striation of the fingernails and hyperkeratosis of the soles. The patient, a man aged 39 years, had Hodgkin's disease. There was a history of night blindness, but the diet had been satisfactory. A microscopical examination of the skin showed atrophy of the epidermis, with abnormal wrinkling and excess of keratin. There was a reduction in the amount of melanin in the basal layer. A slight degree of perivascular cuffing with chronic inflammatory cells was evident in the superficial layers of the corium. The picture was suggestive of vitamin deficiency. Plasma analysis showed a diminution in the amount of carotene and of vitamin A. The presence of the latter in the urine was of pathological significance. The liver was enlarged, doubtless due to lymphadenomatous infiltration. Hippuric acid tests indicated a severe impairment of hepatic function, and this disorder must have been the main factor responsible for the dysvitaminosis. The patient was given a course of injections of vitamin A. The skin seemed to derive benefit from this therapy, but the case eventually proved fatal.

Diagnosis and differential diagnosis

Biopsy and necropsy

Relationship to lymphosarcoma and reticulum cell sarcoma—Herbut, Miller and Erf describe 6 cases which at one time were diagnosed as Hodgkin's disease and at another as lymphosarcoma and which at necropsy showed various combinations of Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma. In a typical case biopsy of a lymphatic gland led to a diagnosis of Hodgkin's disease but a gland removed one year later was diagnosed as lymphosarcoma. Over 2 years later a third gland showed Hodgkin's disease with typical Sternberg Reed giant cells. Subsequently at necropsy, the changes of lymphosarcoma were present in some glands, those of Hodgkin's disease in some, and of reticulum cell sarcoma in others. The cellular composition of the glands in some patients was at times so mixed that it was impossible to label the tumour precisely. The authors point out, in common with earlier observers, that these various combinations can be explained only by considering the 3 diseases as arising from a common stem cell, the reticulum cell, and then differentiating in one direction or another according to the type and the amount of cell stimulation. It has been shown that there are two substances, one of which is specific for stimulating the proliferation of myeloid cells, the other specific for lymphoid cells. They appear to be mutually reciprocal in action. The myeloid stimulator causes maturation of lymphoid cells and vice versa. These substances both appear in equally increased amounts in the urine of patients with Hodgkin's disease and monocytic leukaemia and when injected they cause pleomorphic lesions in the organs of guinea-pigs. By chemical separation, the substances which elicit increased lymphopoiesis have been identified as carbinols and those which cause increased myelopoiesis as non-carbinols. Proliferation arising because of an excess of the lymphoid stimulator produces a rise to Hodgkin's disease when the stimulation is accompanied by maturation, or to reticulum cell sarcoma when it is unaccompanied by maturation. Combinations of these diseases result either when the specific stimulators are not uniformly distributed throughout the organs or when a temporary excess of one is followed by a temporary excess of the other.

Glazebrook, A. J., and Tomaszewski, W. (1944) *Arch. Derm. Syph.*, N.Y., 50: 85.

Herbut, P. A., Miller, F. R., and Erf, L. A. (1945) *Amer. J. Path.* 21, 233.

Wolpaw, S. E., Higley, C. S., and Hauser, H. (1944) *Amer. J. Roentgenol.*, 52: 374.

HYDATID DISEASE

See also B.E.M.P., Vol. VI, p. 538, and Cumulative Supplement, Key Nos. 692-701.

Miscellaneous cysts

Cysts of the heart

Difficulties in diagnosis—Peters, Dexter and Weiss have collected from the literature 56 cases of echinococcus infestation of the left side of the heart and have added 5 new cases. Although this is a rare disorder, surgery with improved technique in thoracic exploration promises some hope of relief. The mode of transmission of the larvae of *Echinococcus granulosus* from the dog intestine to the human being is in some doubt but is assumed to be by way of the digestive tract. It has been suggested that infestation occurs probably almost entirely in childhood. The larvae enter the portal circulation and some survive to form cysts in the liver. Those which pass the liver filter enter the heart and pulmonary tree in which about one-third of the number are retained; the rest pass into the systemic circulation to form cysts in muscles, spleen, kidney, brain and bone. Cardiac cysts are formed by the entrance of larvae into the coronary arteries, more commonly the right than the left. These cysts may fibrose and calcify, remain alive and intact in the heart or rupture into the pericardium or chambers. In the latter event the cyst contents may occlude arteries, particularly large ones, disseminate germinal

elements into the peripheral tissues and give rise to severe systemic disturbances through the liberation of protein into the circulation. Living intact heart cysts tend to be asymptomatic and may be detected only by means of x-ray examination. The indications, should they be detected, are for surgical exploration and extirpation for the purpose of preventing rupture. The effects of the cysts on myocardial function, valvular efficiency and conduction are not well recognized, although in one case the electrocardiogram was normal except for a minimal depression of the S-T segment. In only 6 of the 56 cases was a diagnosis made *ante mortem*. Skin and serological tests and eosinophil estimations are indicated, just as they are in the case of suspected cysts elsewhere, but sudden anaphylactoid collapse or hydatid embolic phenomena are often the first indications of a cyst in the heart. When the decision to operate is being taken two important factors must be borne in mind. The first is that secondary intracranial cysts from previous rupture contra-indicate interference since they themselves cannot be eradicated, and the second that a differential diagnosis must be made between cardiac cysts and pulmonary cysts adjacent to the heart.

Peters, J. H., Dexter, L., and Weiss, S. (1945) *Amer. Heart J.*, 29, 143.

HYGIENE AND PUBLIC HEALTH

Hygiene

Personal hygiene

The menstrual tampon.—Widenius investigated the use of 6 types of commercially manufactured menstrual tampons among 25 women of varying ages and pelvic types, of whom 9 had previously experienced their use. Five women subsequently became pregnant, indicating that the use of tampons does not prevent conception. Cervical erosions were found in 7 women, of whom only 2 had previously used tampons. The aetiology in these 2 cases was respectively a lacerated cervix after childbirth and a congenital erosion. Of the 6 tampons, 4 were designed for manual self-insertion and 2 for use with individual inserters. The use of an inserter permits proper placement of the tampon within the vaginal tract without contamination by the fingers. Three tampons were of non-expanding type with a fixed length, the shortest, No. 1, being $1\frac{3}{8}$ inches long. Tampons No. 3 and No. 4 were over 2 inches long. Discomfort was less frequent with shorter tampons, which are least likely to cause pressure against or displacement of the cervix. Tampon No. 2, $2\frac{1}{8}$ inches long, expands laterally only. Tampons No. 7 and 12, measuring respectively 4 and 2 inches long before compression, after insertion can expand both laterally and lengthwise. Swabbing of vaginal walls and cervix with a preparation of sodium tetraiodophenolphthalein (iodophthalein) and gum acacia and dusting of tampons with powdered barium sulphate before insertion allows x-ray visualization of the tampons in use during menstruation. Tampons 2 inches long are shown to be those least likely to deflect the cervix. The general conclusion is that catamenial tampons can safely, comfortably and adequately control an average menstrual flow in an average woman, provided that a short tampon, preferably having a rounded base to allow easy removal, is properly placed well within the introitus. Adequacy of protection can be judged only by correlating the length of complete protection with the actual weight of absorbed menstrual blood within the tampon.

Social medicine

Importance of vital statistics in education

Crew, in a lecture delivered at Edinburgh, stressed the importance of the prevention and treatment of disease which is engendered by disharmony between man and the social structures he has created. Such an aim necessitates an expanding scientific knowledge of man and of society. The medical faculties of universities, therefore, are now finding a place for social medicine, which is defined as medical science in relation to groups of human beings. The department of social medicine must comprise more than specialists in public health and in industrial medicine. It must include specialists in demography, physical medicine, social biology, anthropology and psychology. A student of social medicine requires a knowledge of vital statistics and of the environment in which the causes of disease are likely to be found. There is an urgent need for data concerning morbidity as contrasted with mortality. The Army, with its comprehensive system of medical inspection and care, has provided a model for social medicine. The new science of human oecology has proved to be of the greatest value and must be encouraged for the purposes of peace. Another important problem is concerned with the assessment of the agencies that determine positive health in a community. The problem is within the scope of field physiology, using the statistical techniques of psychologists and industrial efficiency experts in order to assess the significance of biochemical and physiological tests of physical fitness. Performance tests are of value in determining whether or not the individual is fit for employment, since many disabilities are due to dissatisfaction with the environment. The tests are designed to measure the individual's inherent and acquired qualities. The factory, the nursery school and the youth services form examples of subjects which provide facilities for the study of individual and social variables. These variations have profound repercussions on our views concerning such matters as rehabilitation, vocational guidance, town-planning and distribution of population.

Role of the doctor

Cilento gives an account of the pronouncements made by the English Royal Commission

of 1869 At that time emphasis was laid upon various prohibitions such as the prevention of the pollution of water and the removal of nuisances In contrast, modern public health practice requires living standards based on personal and intimate services in the interests of the individual and of the community It is the province of social medicine to bring these living standards to the forefront of the whole problem of medical care There must be a correlation of protective and corrective measures for health The responsibilities both of the medical student and of the medical graduate in relation to the community require continued expression in lectures and practical demonstrations Research work must be consistently maintained by the State and financial provision should be made for every communal activity for the prevention of disease and the treatment of infection The activities of social medicine must also be directed towards the serious problem of the decline in the birth rate If the practice of medicine is to be a service for health and not for disease, there must be a close cooperation between the general medical practitioner and the State The essential basis of the cooperation is group practice within a loosely linked governmental organization, and the medical group should be allowed the greatest possible autonomy Joint consultative health centres should be set up in every town From 15–20 medical practitioners should practise at each centre serving a population of 30,000 The group should appoint its own superintendent, who would be directly responsible to the government or controlling body No system will last, however, if an attempt is made to interpose any lay person between the patient and the medical practitioner

Prophylaxis

Veneral diseases

Shiels describes the part that the general practitioner may play in the cure and prevention of venereal diseases Modern methods of treatment if applied early, are effective and in time should make the occurrence of such diseases rare Between World War I and World War II the general practitioner did not take a prominent part in the national effort to reduce the incidence of venereal diseases Treatment was carried out mainly at clinics at which it is free of cost, confidential and under specialist supervision Wartime increase of the diseases public lectures, newspaper publicity, radio discussions and special films have brought the broad facts to the notice of a much wider public Practitioners already trained in the prevention and cure of venereal diseases in the Forces and those who could be trained by short courses at a clinic will in future be able to diagnose and treat these diseases with knowledge and with confidence Treatment of gonorrhoea with sulphonamide drugs is well within the scope of the practitioner In his work he would be closely associated with the medical staff of a clinic for any specialist type of work as well as for tests to establish whether or not a cure has been made In regard to venereal diseases, laboratory services are free of cost to the patient The practitioner should endeavour to bring under treatment the contacts of his patients, for instance the wife of an infected husband The patient should be made to understand that information about contacts is an urgent matter of public health and that the tracing of them has no punitive purpose The practitioner is in a much better position than is the clinic to give continuous treatment to patients since they are less likely to avoid the consulting room than they are to avoid the clinic In regard to fitness for marriage and parenthood the practitioner is in an excellent position to advise a thorough examination, including blood tests for seronegativity, so that the birth of congenitally syphilitic children may be prevented The question of prophylaxis is a difficult one, in the armed forces prophylaxis is justified, but conditions in civil life are less favourable for its practice With regard to propaganda, health subjects especially those relating to sex the practitioner is well placed to influence the youth of his district

Cilento, R (1945) *Med J Aust*, 1, 25

Crew, F A E (1944) *Lancet*, 2, 617

Shiels, D (1945) *Practitioner*, 154, 273

Widenius, Irja E (1944) *Amer J Obstet Gynec*, 48, 510

HYPERCHLORHYDRIA

See also B E M P, Vol VII, p 1, and Cumulative Supplement, Key No 708

Physiology, pathology and pathology

Experiments on dogs

Hydrogen ion concentration of duodenal contents and its reaction on gastric secretion —Pincus Friedman, Thomas and Rehfuess describe a quantitative study, by experiments on dogs with a Pavlov pouch of the inhibitory effects upon gastric secretion of the hydrogen ion concentration of the duodenal contents They claim that their results refute the suggestion that the intestinal phase of gastric secretion is normally regulated to some extent by the acidity of the duodenal contents, at any rate in the dog little if any inhibition of acid secretion occurs if the intestinal pH is above a threshold of 2.5, but as acidity as great as this is, according to previous experimenters, rarely present in the dog's intestine after a test meal, the authors regard inhibitory effects upon gastric secretion by such a degree of duodenal acidity as an emergency mechanism which arrests the secretion of acid at its source and which therefore operates only when other, presumably normal, means of reducing duodenal acidity have failed and when the acidity of the duodenal contents attains a degree harmful to its mucosa The fact is emphasized that the threshold level of duodenal pH for the inhibition of gastric

acid secretion is within the pH range of the contents of the antrum of the stomach. Pincus and his colleagues suggest that the normal mechanism consists probably in a rapid dilution and partial neutralization of the chyme by an accumulation of duodenal contents in the vicinity of the pylorus which occurs when the stomach contents enter the intestine. They describe experiments in which mere intestinal distension by large volumes of acid fluid failed to inhibit gastric secretion if the degree of intestinal acidity was kept below threshold level. They claim also to have proved that although gastric secretion stimulated by nervous factors, insulin and the placing of food in the stomach through a gastric fistula (with careful avoidance of conditioned reflexes) was inhibited by the setting in motion of the emergency mechanism by the introduction of excess acid into the duodenum through an injection tube, this procedure failed to affect histamine-induced gastric secretion.

Pincus, I. J., Friedman, M. H. F., Thomas, J. E., and Rehfuess, M. E. (1944)
Amer. J. digest. Dis., 11, 205.

HYPERIDROSIS

See also B.E.M.P., Vol. VII, p. 25; and Cumulative Supplement, Key No. 709.

Physiological considerations

Emotional sweating

The ferric chloride test.—Silverman and Powell discuss the clinical significance of a palmar sweat response obtained from more than 1,100 military patients. They maintain that palmar sweating, which is not influenced under ordinary conditions by outside temperatures, is a cholinergic phenomenon and is an indicator of emotional and mental disturbances. The method used for testing was to apply a prepared solution of ferric chloride to the skin and then apply paper treated with tannic acid which interacted with the ferric chloride carried into solution by the sweat to produce a stain varying from grey-blue to blue-black according to the intensity of sweating. The authors review the present knowledge of the nervous pathway involved in sweating which suggests that the cerebral cortex and diencephalon are both concerned with sweat impulses. In the spinal cord, sweat fibres originate from the cells of the lateral horn and travel along the sympathetic trunk. Pharmacologically, sweating behaves as a parasympathetic mechanism; for example, it is stimulated by acetylcholine and inhibited by atropine. The authors cite the observation of Gellhorn that emotional excitement stimulates both branches of the autonomic nervous system, and they question the principle of reciprocal innervation, pointing out that it is practically impossible to find a pure example of vagotonia or sympathicotonia. Silverman and Powell state that palmar sweating has not the usual thermo-regulatory or excretory significance of general bodily sweating and that it occurs particularly in anxiety neurosis, in the DaCosta syndrome and in neurocirculatory asthenia. In their patients in whom the test elicited an intense response there was evidence of emotional strain, and the men made poor soldiers and were often in hospital.

Silverman, J. J., and Powell, V. E. (1944) *Amer. J. med. Sci.*, 208, 297.

IMMUNITY AND IMMUNIZATION

See also B.E.M.P., Vol. VII, p. 58; and Cumulative Supplement, Key Nos. 720–733.

Active immunity

Antibody

Lymphocytes and the formation of antibodies.—Harris and his colleagues describe experiments in which rabbits were injected with either sheep's erythrocytes or an antigen prepared from typhoid bacilli. The efferent lymph from the popliteal lymphatic gland was collected during the period of rising titre. Immediately after collection the lymph was centrifuged and the plasma was drawn off. Analysis proved that the titres in the cell extract were consistently higher than were those in the plasma; the difference was often of considerable magnitude. There was no precise pattern in the ratios between the respective titres of lymph plasma and cell extract, but the ratio was greatest on the fifth day, when the most considerable rate of increase in antibody titre occurred in the lymph. The titres in the lymph plasma were higher on the sixth and seventh days than they were on the fifth day. The findings were consistent with a primary appearance of antibodies within or on the surface of the lymphocyte, and inconsistent with what would be expected if the opposite were true. In another experiment the lymphocytes were brought into prolonged contact with the plasma *in vitro*. It was found that the titre in the cell contents fell sharply to approach that of the supernatant fluid. Apparently the antibodies which had been within the lymphocytes, or on their surface, had escaped into the plasma. Similar results were obtained from experiments *in vivo* in which normal lymphocytes were incubated with lymph fluid and antibodies. It is concluded that lymphocytes are instrumental in the formation of antibodies.

Cellular immunity

Importance of gamma-globulins in lymphocytes.—The human serum γ -globulin fraction contains almost all the antibody activity of pooled plasmas and there is little doubt that antibodies are modified serum globulins, in man chiefly modified γ -globulins. Kass reports the preparation of rabbit antisera to practically pure γ -globulin fractionated from pooled normal plasmas. A specific reaction occurred with these antisera and human lymphocytes. It is already known that antibody exists in the lymphocytes of rabbits and mice. Mesenteric lymphatic glands were obtained from a human being at necropsy, and were suspended in

saline and filtered. The lymphocytes in the filtrate were then centrifugalized and washed, resuspended and frozen and thawed until lysed. The supernate after further centrifugalization precipitated with the rabbit antiserum prepared against γ -globulin and failed to react with normal rabbit serum. Diluted lymphocyte extract, when mixed with the serum, inhibited the ability of the antiserum to precipitate purified human γ -globulin. The occurrence of normal γ -globulin in lymphocytes coupled with the demonstration of lymphoid hyperplasia accompanying antibody production and the failure of lymphocytes to absorb antibody *in vitro*, suggests that the specific alteration of γ -globulin to cause the molecule to become reactive towards a given antigen occurs within the lymphocyte.

Passive immunity

History of serology

Parish reviews the history of serology over half a century. He states that the study of antitoxins and their properties dates back to the work of Behring and Kitasato in 1890. In 1894 Roux published his classical paper on the treatment of diphtheria and in the same year 20 cases of diphtheria were treated with his serum in Great Britain. In the attempted preparation of antitoxin on a large scale, practical difficulties arose owing to reactions which followed the injection of increasing amounts of toxin. After the work of Behring and Wernicke the toxin-antitoxin method of immunization was developed. Theobald Smith in 1909 first suggested the use of toxin-antitoxin injections for the immunization of children. The modification of toxin by the addition of formalin to form toxoid was in use in serological laboratories in 1904. Diphtheria immunization received a considerable setback by the occurrence of three disasters—the last two in the years 1924 and 1925—which were due to the fact that toxic mixtures were injected instead of properly balanced antitoxin-toxin mixtures. In Great Britain in 1924 toxoid-antitoxin mixtures were in use, but they were superseded by two more potent antigens: toxoid-antitoxin floccules (T A F) and alum-precipitated toxoid (A P T). The discovery of the latter, with the use of the proper spacing of doses, has been of great importance in the preparation of antiserum and in the active immunization of man. Great progress has been made in methods of standardization. Romer's evolution of the intradermal diphtheria virulence test in guinea-pigs was followed by the development of the Shick test in 1913, and thereafter Ramon introduced a flocculation method. These and other discoveries made possible the Therapeutic Substances Regulations of 1931, in which antitoxins and sera are controlled and standardized against British standards, which in their turn are advanced. A method of salting out with ammonium sulphate was found which gets rid of the non-specific proteins and a further method of purification by enzyme treatment, the advantages of which are considerable, has been made known. In the recent war tetanus giving of toxin, not toxoid, since the addition of formalin to the toxin destroys both toxicity and antigenicity. In the case of staphylococci the complexity of the toxins provides many problems, some of which remain to be solved. Parish concludes that complexity is the hallmark of serology—the deeper research goes the more intricate the methods of attack and defence are. He believes that future work on serology will be well worth while. Chemotherapy is not the final answer in the control of infection, in support of this the author instances the growing incidence of reported drug-resistant strains of bacteria.

Practical applications of immunity

Multiple immunization

Hamilton and Knouf, recognizing that active immunization against diseases of childhood is no longer questioned by the medical profession nor by a large section of the public, advocate the triple injection of prophylactic against diphtheria, tetanus and pertussis. The combination of diphtheria and tetanus toxoids in one injection has proved to be a desirable and practical application of multiple immunization. The authors set out to study the results of combining these toxoids with a concentrated pertussis phase I vaccine. The material was detoxicated, sterilized and purified and phase I pertussis vaccine was added, the final concentration giving the usual dosage of the 2 toxoids with 40 000 million pertussis organisms per cubic centimetre. Toxicity and immunity tests were carried out on animals before 64 children from private practice mostly between 12 and 15 months of age were injected subcutaneously in the deltoid region at monthly intervals for 3 injections. Reactions were practically non-existent, although mothers were advised to look out for untoward symptoms. Neither nodules nor lumps were found. In cases subsequent to this series, the 2 toxoids were adsorbed on to aluminium hydroxide and painless nodules occurred rather often. Clinical proof of the triple injection must await the passage of time. Laboratory investigation of blood serum carried out 3 months after the last injection will give evidence of the degree of immunity, which is indicated by agglutination and titration tests. The authors remark on the decrease of parental reluctance against this form of multiple immunization, implying that the allurements of the triple injection outweighs the objection to a one-disease immunization.

Hamilton, P. M. and Knouf, E. G. (1944) *J. Pediat.* 25: 236.

Harris T. N., Grumm, E., Mertens, E., and Ehrlich, W. E. (1945) *J. exp. Med.*, 81: 73.

Kass, E. H. (1945) *Science* 101: 337.

Parish, H. J. (1944) *Proc. R. Soc. Med.*, 38: 1.

IMPETIGO

See also B.E.M.P., Vol. VII, p. 81; and Cumulative Supplement, Key Nos. 734 and 735.

Acute impetigo**Treatment**

Good effect of calamine liniment.—Smith and Jones describe treatment of impetigo with calamine liniment and emphasize some objections to local sulphonamide therapy which, like treatment with mercurials and dyes, may disastrously aggravate the condition. Moreover, unsuccessful sulphonamide therapy may not only lead to sensitization but may render subsequent cure more difficult. The authors' method depends upon the meticulous application of 6 principles: (1) free exposure (by shaving if necessary) of all parts to treatment; (2) avoidance of trauma, except that inseparable from shaving; (3) dressings kept continuously moist and in close apposition with the affected parts; (4) removal of the dressings only for the minimum time necessary for shaving or re-dressing; (5) inclusion of every outlying lesion under the dressing which should extend an inch or so beyond the affected area; (6) change of treatment from compresses to smears as the condition may demand. The authors describe the ruthless shaving of all hairy parts as being the key to success, and say that it is necessary to protect tender parts and to soften crusts by first anointing the parts concerned with Lanette wax SX base ointment. The bearded area must be shaved every second day. Jaconet, as a covering dressing, retains moisture and thus constituted an economy in labour and material, but it is contra-indicated in hot weather and in the presence of acute inflammation. The Lanette wax base ointment contains: Lanette wax SX, 10 parts; Vaseline, 10 parts; water to 60 parts. The modified calamine liniment (to economize oil) is composed of wool fat, 2½ oz.; Lanette wax SX, 2½ oz.; calamine, 3½ oz.; olive oil, 20 fluid oz.; water to 80 fluid oz.

Smith, Mary S., and Jones, E. C. (1945) *Brit. med. J.*, 1, 699.

IMPOTENCE

See also B.E.M.P., Vol. VII, p. 103.

Treatment*Artificial insemination*

Barton, Walker and Wiesner give an interim report to clinicians on artificial insemination with husband's semen and with donated semen. In case of male impotence, dyspareunia, ejaculatory failure and defective cervical invasion, artificial insemination with the husband's semen may be carried out, after attention to any fecundity defects of the wife. In cases coming under the first three headings, self-insemination by the wife is the method of choice. In cases of defective cervical invasion a small quantity of semen should be injected very slowly into the cervical canal. Donated semen may be used in cases of incurable male sterility and for genetic reasons. Great care must be taken in the choice of donors, and complete anonymity preserved. The donor should have at least 2 legitimate children, be of mature age—30–45 years—in good health and with no history of transmissible disease. Excessively pronounced physical features are undesirable. The fecundity and viability of the semen should be great and the donor's blood group should be identical with that of one parent. The actual process of cervical insemination is without danger provided no air is injected and no semen allowed to enter the uterine cavity. Semen infected with pathogenic organisms, however, constitutes a danger, and there may be impairment of the normal cervical defence; for this reason intra-uterine insemination is dangerous. Subfecund semen might cause dysgenic conception and in any interference with the semen there is a risk of adverse affection of the progeny. There is, too, always the danger of psychological damage to husband and wife, and careful initial selection of cases is necessary.

Barton, Mary, Walker, K., and Wiesner, B. P. (1945) *Brit. med. J.*, 1, 40.

INDUSTRIAL ACCIDENTS

See also B.E.M.P., Vol. VII, p. 118; and Cumulative Supplement, Key Nos. 738–748.

Hazardous occupations*Dangers of x-ray and radium emanations*

Browning describes the injuries that may be sustained by workers who are exposed to radiations such as x-rays used for detecting flaws in metal articles. An x-ray burn may produce a transitory patch of erythema or chronic ulceration, but it is probable that a single burn never initiates cancer. Chronic x-ray dermatitis is a precancerous condition, however, and consists of a combination of atrophic and regenerative processes. Skin reactions may appear some time after exposure has ceased and include telangiectasis, warts and ulceration. Inadequate protection may cause sterility and blood changes ranging from leucopenia to aplastic anaemia and leukaemia. Screening is more dangerous than is photography and scatter radiations require special precautions. Preventive measures include attention to general hygiene and working hours (35 hours a week and 4 weeks' holiday yearly, are suggested), and the provision of lead screens, protective clothing and mirrors. α particles are the most destructive but are the least penetrating of the three types of radium radiation. β particles chiefly produce skin injuries similar to x-ray dermatitis and γ -rays cause aplastic anaemia. The great incidence of lung cancer in the workers at Joachimsthal, Bohemia, is attributed to the inhalation of radon emanating from the radium chloride in the uranium ore. True radium poisoning occurred in the luminizers of New Jersey, in whom aplastic anaemia, jaw necrosis and malignancy

has been recoverable. It is now known that there is a group of A viruses with a serological relationship to the virus of swine influenza and a group of B viruses distinct antigenically and with no apparent immunological relationship to the A viruses. Ferret inoculation and observation is the classical method of studying a suspect virus and, should inoculation fail to induce signs of infection, the development of specific antibodies may still be detected. Methods of measuring the rise in titre of antibodies during the illness, complement fixation tests and the estimation of antibodies capable of inhibiting erythrocyte agglutination by the virus have all, however, yielded valuable information. Infection with influenza A usually produces an illness in which the common influenzal symptoms occur but in which the patient can be classified approximately in one of three groups. In the first, pharyngitis and tracheitis occur without clinical signs of lung involvement, in the second bronchitis and bronchiolitis without consolidation, and in the third demonstrable consolidation. It appears to be most likely that secondary bacterial involvement, notably by the pneumococcus and by *Staphylococcus aureus*, is necessary for the production of consolidation. In influenza B lung complications occur much less often. The mechanism of immunity to influenza is a complex process in which the production of antibodies plays only a part. Other factors are related to the innate resistance of the mucosa of the respiratory tract which possesses methods of defence by virtue of the nasal secretion in addition to more definitely cellular activities. Two distinct lines of attack have been made in experiments designed to produce active immunity. One is the use of a virus vaccine subcutaneously, based on the assumption that most individuals have been subject to nasal infection by the virus and that all that is needed is reinforcement of a waned immunity. The second method is the use of an attenuated virus strain intranasally. In the general control of influenza methods of aerial sterilization appear to be of great importance.

Notes on 1943 epidemic.—Epidemics of influenza in Great Britain have of late years begun in the early winter months. In 1943, however, the amount of influenza prevalent in the early months of the year was small and was largely due to influenza virus B. There was a widespread outbreak in the autumn of the same year which was investigated serologically by Andrewes and Glover, who found that the infection in this period was due to influenza virus A. Their enquiry into localized summer outbreaks in the same year yielded the same conclusion. The first test was used, which involves the inhibition of agglutination of fowl erythrocytes by influenza virus. Serums were taken from clinically typical cases widely scattered throughout the country, and rises in the titre against influenza B virus were not found. Ferrets were inoculated with unfiltered garglings from 24 patients. Typical symptoms were produced from 14 of these. Unlike results attained in the last few years the symptoms were, generally speaking, quite distinct, and the virus was readily transmitted in series. These findings confirm the suggestion that there is a correlation between the extent of epidemic spread in man and the ease of inducing infection in ferrets. The strains isolated were not easily adapted to the mouse, and not at all to the chick embryo.

The problem.—The epidemiological aspects of influenza are, says Greenwood, of little value to the general practitioner. More knowledge is accumulating yet it is not possible either to predict an epidemic or a pandemic or to anticipate the character of the disease, whether mild or severe. For statistical purposes, a wide definition of influenza is necessary which will include systems other than the respiratory. There is some evidence to support the view that agues and "nervous" diseases such as encephalitis and poliomyelitis, are prevalent before and after influenza epidemics. General misery has always prevailed before outbreaks of typhus. It is not so with influenza. The majority of great influenza epidemics reach their peak towards the end of winter, and are killing diseases; summer epidemics are much less fatal. The force of an epidemic is usually spent in 7–10 weeks, the death rate rising steeply in the first few weeks and afterwards declining gradually. It seems to be established that a measles epidemic will pass off before all susceptible contacts have acquired it. This may be due to subclinical infection conferring some immunity. The intensive study of influenza has revealed a much more complicated problem than was anticipated. The epidemic of 1918–1919 is unique; 3 epidemic waves were compressed into little more than 6 months. It is suggested by some authorities that modern social habits favour the onset of epidemic influenza, since masses of the population work in cities and large towns and reside in suburban areas. Greenwood comments on the absence of epidemic influenza despite wartime overcrowding.

Bacteriology

Size of virus particles.—The density and size of virus particles in solution can be ascertained from measurements of rate of sedimentation through media of different densities. Rate of sedimentation in concentrated solutions changes rapidly with time. In order to obviate this difficulty, Sharp and his colleagues, when investigating influenza virus A (PR8 strain) employed solutions of bovine albumin, of great molecular weight and of low osmotic pressure. The albumin was added to a purified preparation of the virus. The sedimentation rates were then measured at intervals over a period of 28 hours. No significant change in the rate was observed over a period of 2.5 hours. For comparison, the effects of sucrose in 11 per cent concentration and of about the same density were ascertained. Sedimentation rate of the virus increased rapidly from the start to attain in 2.5 hours a level 10 per cent greater. A series of measurements were made on solutions of the same virus and salt content but of albumin content varying from 0 to 25 per cent. Calculation made from these sedimentation rates gives

for the radius of the sedimenting particle a value of 57.7 millionths of a micromillimetre, a diameter of 115 millionths of a micromillimetre, which is slightly larger than that recently reported, 101 millionths of a micromillimetre, from electron micrographs. The procedure employed provided a method for the direct determination of the density of virus particles in solution.

Immunity

Variation in antigenic strength of virus A—Magill and Sugg report on data demonstrating that antigenic differences may occur in strains of the A group of influenza viruses. Mouse-protection tests were performed against 7 different strains of virus using sera from 40 patients with influenza. Six strains were representative of group A but the seventh belonged to group B. Two samples of serum were obtained from each patient. The first specimen was taken in the early stages of the illness and the second 2 or 3 weeks later. It was found that the calculated antibody titres were influenced by the strain of virus used for testing the sera. There was a noticeable difference between the results obtained with group A and group B, as was to be expected. There were, however, also pronounced differences amongst the 6 strains of group A. The investigation has a bearing on the diagnosis of influenza by the demonstration of an increase in the titre of serum antibodies. The results show that the number of cases diagnosed as influenza would depend upon the strain of the virus used to test the sera and also upon the basis of tests against several combinations of strains included within group A.

Clinical picture

Complications

Use of penicillin—Lescher describes the complications of influenza. Infection is due to a filter-passing virus. In some epidemics this virus is labelled A, in others, B, there is probably a variety of strains not yet labelled. After infection, neutralizing antibodies have been demonstrated in human and in ferrets' blood. Subclinical infections occur during epidemics, the virus passing from host to host with increasing virulence. Complications are due to super-added infections of the lower respiratory tract by other pathogenic organisms. The condition which arises may be unilateral or bilateral and is usually at the base. Toxicity, cyanosis and obstructive dyspnoea are the features of severe capillary bronchitis. With extension downwards of a pure virus infection, atypical pneumonia may result, running a benign but protracted course. When it is complicated with pneumococci, streptococci or staphylococci the course of the disease varies from mild to very severe and may prove to be fatal. Pneumonia may start with a rigor, with few physical signs and with only a little scanty blood-stained sputum. Haemolytic streptococcal infection is very dangerous, with thin purulent sputum salmon pink in colour, cyanosis and extreme toxæmia. Pleural effusion may occur rapidly and may easily be overlooked. Influenzal infection may affect the peripheral vascular system, and thus may lead to a variety of sensations and initiate an anxiety state, the heart itself not being considered to be the real seat of the trouble. It is probable that the nervous system can be affected by the influenzal virus, causing neurasthenia and mental depression. There is no convincing evidence that a specific treatment has yet been evolved. Treatment of complicated influenza is determined by the nature of the complicating organism, and is usually with continuous intramuscular drip, 20 000 units in 3 hours is used when sulphonamides fail in haemolytic, pneumococcal and staphylococcal infections.

Treatment

Preventive

Duration of immunity—Hirst, Rickard and Friedewald discuss duration of immunity induced against influenza by inactive virus. Recent evidence by the American Commission on influenza suggested a 75 per cent reduction of incidence, when the period between epidemic and fluid by adsorption on and elution from embryonic erythrocytes. Other published results were vitiated by variations beyond sampling error amongst different groups of patients. The present report is on a group of individuals vaccinated between 11 and 14 months prior to epidemic with similar, formalin killed material. Serological evidence indicated that the vaccinated individuals possessed three times as much circulating antibody at the time of the epidemic as they had before vaccination, and in seven different institutions which had been selected for the test, these individuals displayed a lower attack rate than did the unvaccinated controls. Formalin killed vaccine, administered shortly before an epidemic, produced a marked reduction in attack rate. The evidence in the present investigation and also in one conducted in 1941, when a weak preparation was used, indicated that the peak of immune effect declined rapidly. In the case of the weak preparation no clear-cut immunity was apparent after 8 weeks, the maximum effect of a concentrated and more potent preparation had declined notably by the seventh week but then persisted at a lower level for a year. The results suggest that vaccines of this type should be administered in the face of an outbreak rather than in advance of the epidemic season.

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INJURIES

Wounds

Infections and complications

War wounds and clostridia.—Cooke and his colleagues report on their observation over a period of 4 months of 2,680 wounded soldiers treated at the Queen Elizabeth Hospital, Birmingham. Amongst these were 76 patients who were suspected, because of systemic reaction, of having clostridial infection, and who were kept under particularly close observation. The reactions noticed were characterized by a sallow, cyanotic complexion, drowsy irritability, anorexia and clammy skin, and persistent local discomfort in the wound was also regarded as an indication for the making of further investigations. Since clostridial organisms were actually obtained from 72 wounds it is suggested that the group of 76 patients included the great majority of true and potential gas gangrene cases of the whole series of 2,680 wounded men observed. From each of 4 subgroups, which included 24 patients with mild systemic reaction, 41 moderately ill, 9 dangerously ill and 2 fatal cases, illustrative case reports are presented. Biopsy of non-contractile, brick red or poorly bleeding muscle obtained from the wound depths of both fatal, 7 severe and 18 moderate cases, showed the histopathological appearances of clostridial myositis, namely a zone of necrosis, a surrounding zone of degenerated muscle fibres and disappearance of connective tissue and, peripherally, capillary dilatation and haemorrhage. *Clostridium perfringens* was the most often recovered pathogenic organism. *Clostridium septicum* and *Clostridium oedematiens* were not obtained. Low blood cholesterol and high urine creatinine levels were regarded as being possibly significant biochemical findings. Severe haemolysis did not occur and acidosis was not observed more often than in the other wounded. Demyelination of the central nervous system—in particular of the optic nerves of one patient who became blind shortly before death—and extensive fat embolism involving the lungs and other organs, were demonstrated in the 2 fatal cases. In discussing the possible relationship of the clostridial infection to the systemic reactions observed, the authors suggest that the products of tissue breakdown may be a more important factor than the circulating toxin. This would explain the lack of dramatic effect with antitoxin, unless it is given early and abundantly in order to prevent tissue destruction by clostridial toxins. Surgical removal of necrotic muscle is thus an essential procedure.

Traumatic uraemia.—Parsons reports on 2 cases of traumatic uraemia. Both were in healthy young soldiers who sustained extensive limb wounds with so much muscular and vascular damage that amputation was necessary. Surgery, penicillin and sulphonamides controlled infection but uraemia developed rapidly and was the cause of death in one case. In the fatal case the kidneys at necropsy were slightly oedematous, there was little fatty change, the glomerular tuft was congested but not grossly abnormal, and some tubules were dilated and contained hyaline and granular casts. In the surviving patient, kidney function was normal when it was examined subsequently by the generally accepted tests, but simple water dilution and concentration tests showed there to be a defect. The author is of the opinion that in severe injuries of an extremity with damage to the large vessels, traumatic uraemia may be relatively more common than it is generally believed to be. It appears to be probable that the rise of blood urea is caused by an increase of urea formation from tissue protein after severe traumatic haemorrhage and that urea retention is occasioned by impaired renal function due to anoxia. In the fatal case the necropsy findings in the kidney were similar to those described in other cases. Treatment is still a matter of discussion: theoretically it would appear that treatment should be directed towards the improvement of the blood supply to the kidney. Although the effectiveness of caffeine in such cases is doubtful, it may be given in full doses without resultant harm. Blood transfusion with carefully matched blood would appear to be most important in the treatment. Fluids are also essential but should be given by the mouth and not intravenously because of the danger of subcutaneous and pulmonary oedema.

Sulphonamide therapy.—In assessing the value of a method used to shorten the healing time of various types of contaminated and infected wounds account must be taken of many variable factors, such as bacterial content, type and duration of the wound, condition of the individual and effect of the method on a control wound. Lockwood shows that the efficacy of the method of the application of sulphonamides to wounds, immediately after contamination, is amply supported by experiment. Its higher solubility and diffusibility and freedom from the deleterious effects upon wound repairs have caused the adoption of the immediate use of 5 grammes of sulphanilamide in the wound (with 4 grammes of sulphathiazole given orally) by the United States Army and Navy. Since sulphonamide-inhibiting products of proteolytic degradation are present in abundance in wounds left untreated for 12 hours or more, particularly if putrid saprophytic infection has developed, the likelihood that local application of sulphonamides will influence healing is lessened. There is as yet no evidence of the value of local sulphanilamide therapy in open wounds which have been

subjected to good surgical care. The widespread faith in the effectiveness of locally applied sulphonamides in preventing infections may explain the increasing tendency to undertake primary closure of traumatic wounds in the United States of America in civilian practice, although such closure is deprecated still in military surgery and although figures prove the falsity of such faith. In the treatment of cellulitis with or without sloughs sulphonamides used locally are unavailing and they should be used systemically. Compression dressings appear to have a more important bearing upon the reduction of infection than has the use of sulphonamides either generally or systemically in burns, but a low systemic blood level of the latter for the first few days after a burn may reduce the likelihood of infection. Granulations without superficial infection are not likely to be affected by local sulphonamides to any greater degree than they are by other methods of preparation.

Penetrating ocular injuries and penicillin—A series of experiments in which rabbits with infected ocular injuries were given penicillin treatment is described by Scobee. A virulent strain of haemolytic *Staphylococcus aureus* was used to infect the eyes, and was found to be susceptible to penicillin. The anterior chamber was washed with a solution containing 500 units of penicillin per cubic centimetre of physiological saline, but the method failed to control moderate and severe infections. The results were similar when the animals received 2 intravenous injections daily of 1,000 units of penicillin. Eye drops and subconjunctival injections of a penicillin solution were satisfactory in mild and moderate infections only. The best treatment consisted of penicillin eye drops combined with intravenous injections of the drug. The method effected a cure in all cases except in about 50 per cent of the severe infections. It is recommended that the saline concentration should be 1.4 per cent, because this forms a solution isotonic with the tears and allows greater penetration of the penicillin. On the basis of the experimental work it is suggested that patients with infected ocular injuries should receive 25,000 units of the drug in physiological saline intravenously every 12 hours, it is necessary to combine the treatment with the instillation of eye drops every 4 hours. The drops contain from 250 to 500 units of penicillin per cubic centimetre of solution. The author treated cases of anterior uveitis with daily injections of 150,000 units of penicillin for a period varying from 5 to 12 days. Improvement took place in 75 per cent of the patients, but relapses invariably occurred 1 week later. The inflammatory process was seldom as severe, however, as was the infection present before the initiation of treatment. The outcome was similar in cases of posterior uveitis or chorio-retinitis. When penicillin was administered systemically in daily doses of 150,000 units, chorio-retinal exudates often shrank rapidly in size and there was an accompanying decrease in the size of the scotoma produced by the lesions. Although penicillin is only an adjunct in the treatment of uveitis all patients with the disease should have the benefit of penicillin therapy.

Course and prognosis

Stimulants to healing—Apperly and Cary seek a clue to the discovery of factors promoting the healing process in wounds. They cite equivocal clinical reports. It has been stated that fibroblasts grow best at a hydrogen ion concentration of 7.4–7.8, that increased pH favours healing and increases resistance to tuberculous infection, that external application of dilute solution of ammonium bicarbonate favours healing and that healthy granulation tissue is alkaline, even up to pH 8.3. Contradictory reports state that healing wounds are acid, that acidity promotes healing by limiting bacterial infection, a condition which can be maintained by acid forming diets and by administration of ammonium chloride. The authors investigated rate of epithelization and administered to rats, which were the subjects of experimental skin wounds, 2 per cent solution of ammonium chloride and of sodium acetate in order to produce, respectively, acidemia and alkalemia. Greater concentration of the salts could not be used because they produce nausea and vomiting. After administration of the salts for 25 days it was concluded that in the concentrations used their effects on rate of epithelization were nil. The authors investigated other aspects of epithelization and conclude, as did Henshaw and Meyer, that the rate of proliferation of the basal cells is constant during most of the period of healing and that the times of coverage can be calculated from a simple formula taken into consideration. Apperly and Cary conclude, too, that healing wounds are self-regulating.

Treatment

Skin grafting—Sheehan describes his personal observations on the plasma fixation of full thickness skin grafts. In his technique the patient's own plasma and cell extract are used. At the operation 5 cubic centimetres of blood are aspirated from the patient into a syringe containing 1 cubic centimetre of Tyrode's solution. The mixture is centrifuged and the plasma layer is drawn off and placed in a separate tube. The layer of leucocytes is scraped off with a platinum loop from the residuum in the first tube and is then placed in a tube containing 1.5 cubic centimetres of Tyrode's solution and some glass beads in order to ensure subsequent adequate mixing when the tube is shaken. The graft is cut 20 per cent larger than the defect in order to allow for shrinkage. The base of the area to be grafted is thoroughly cleansed with warm saline solution, lightly treated with a sulphonamide or with penicillin or gramicidin and with a camel hair brush is painted with the plasma. The graft is then painted with the cell extract to which Propamidine or sulphadiazine may be added. The graft is fixed at its lower end to the defect by Michel clamps and is stretched into place by light pressure.

Neither dressing nor bandage is used. Sheehan states that adhesion of the graft is immediate, due to the formation of a fibrin matrix resulting from the interaction of prothrombin in the cell extract and the plasma. The process of recovery of the graft, because of the absence of dressings, may be watched in every stage. When the graft becomes dry it should be covered with sterile yellow petroleum jelly (yellow soft paraffin). When the clamps are removed Cellophane tape is a sufficient dressing for the edges. The author concludes that the use of plasma and cell extracts with bacteriostatic compounds may be of great help in certain situations in surgery such as in the repair of injuries to the face and hands and in the closure of suitable wounds without suture.

Coagulum method of skin grafting.—Harris describes cases in which heterogenous skin grafts were applied by the coagulum method. The method is based on the principles followed in tissue culture in which heparinized plasma is used which coagulates when it comes in contact with tissue extract and salt mixture. When a skin graft is taken, the blood vessels dilate and there is an exudation of plasma. This becomes converted into fibrin which serves to anchor the graft to its bed. The coagulum contact method eliminates these stages, thereby saving 24–48 hours and giving the graft the opportunity of early fixation to the recipient area. The operation is shorter and the hazards of estimating the correct amount of pressure to apply to a graft and the bleeding from an infection of sutures, are eliminated. Harris had good results with heterogenous isografts, with either autogenous or homologous plasma and cell extracts and with heterogenous isografts and stock plasma and cell extracts. The use of stock or homologous plasma is of particular value in extensive burns. Harris notes that the grafts did better on granulating surfaces than on new bases and that grafts on the cheek and one on the pectoral region became dry for an unaccountable reason. The cell extract was painted on the graft while it was still on the drum in order to cover the whole surface thoroughly, and to allow, even after shrinkage, a better chance of agglutination to the entire surface. Impregnated Vaseline gauze was generally used as a dressing, but in infected cases a layer of 5 per cent sulphathiazole ointment was added. In re-dressing, warm saline was applied by irrigation or as a compress for a few minutes beforehand. It is essential to accomplish haemostasis before the grafts are applied.

Healing of skin graft donor areas.—Converse and Robb-Smith report the results of a study of the healing of 469 skin graft donor areas. They find that the quality of the repair was approximately proportional to the rapidity of the healing. The latter depends upon several factors: the thickness of the graft, the thickness of the skin of the donor site, the degree of looseness of the skin at the donor site and infection. The process of healing was studied in detail by biopsies on 4 volunteers. It was found that the epithelium grows out from individual epithelial islands, from hair follicles and from sweat glands; the more numerous the islands the more rapid the epithelization. At the same time each island tends to join its neighbour by contraction; the slower the process of epithelization is the more contracture there is. Thus if epithelization is slow owing to scarcity of islands, infection or mechanical irritation, a thick layer of relatively avascular inelastic fibrous tissue with atrophic epithelium is formed. The authors point out that in assessing the quality of healing of second degree burns it is therefore necessary to know the extent of tissue destruction, and they propose an anatomical classification of burns: (1) superficial burns (epidermal, dermal, deep-dermal and mixed burns) and (2) deep burns (destruction of the whole-thickness of the skin into or beyond the fat). Converse and Robb-Smith conclude that skin grafting in superficial burns is indicated when there is much inter-island contraction such as is found particularly on the dorsum of the hand, on the eyelids or on the face. Skin grafting may be needed too in order to replace skin of poor quality.

Use of fibrin solution in skin grafting.—If early vascularization and survival of a free skin graft is to occur the transplant must be held in complete continuous contact with the surface of the recipient bed. Young summarizes his experiences of fixation of 22 split thickness grafts by the precipitation of fibrin between graft and bed. The rate of fibrin formation can be adjusted to any desired speed by varying the concentration of the solution, obtained by adding thrombin to plasma, which moistens the under surface of the graft. No pressure dressings or sutures were used. The area of skin transferred varied from 4 to 200 square inches, the majority exceeding 30 square inches. In each of 8 cases in which the recipient bed was a fresh surgical wound there was 100 per cent of success. In 4 cases in which the bed was a fresh traumatic contaminated wound, the average take was 48 per cent. On 10 granulating beds a 59 per cent average take was estimated; this was lower than that normally expected. Since they were constantly open to inspection, the progress of the grafts could be observed. In every case loss of graft was apparently due to fluid accumulation under it. Smaller thin grafts have about the average expectancy of take. Young concludes that this method is useful as (1) a quick means of applying grafts on fresh surgical beds, (2) a convenient means of holding grafts in position while compression dressings are applied and (3) a means of applying small grafts such as pinch grafts in cases in which compression dressings are not ordinarily used.

Grafting of mammary gland tissue on wounds.—La Roe has successfully used fresh and preserved breast tissue from pendulous and hypertrophic mammae as a source for heterogenous implants. The tissue was obtained from a patient who was disabled by the great weight of her breasts. Microscopical examination showed no cystic degeneration or malignancy. On removal, the tissue was placed in sterile normal saline. Part of it was used immediately for

surgical replacement of a breast in a case of previous amputation for scirrhus cancer. Post-operatively there was sanguineous and fatty discharge which caused a small cavity. Four-fifths of the implant remained unaffected but required additional sutures to the base of the recipient area. The surplus breast tissue was transferred under aseptic conditions to sterile Tyrode's solution and was kept at a temperature of 45° F. Six days later, a bacteriological test showed no bacterial growth. On the seventh day, part of this tissue was implanted in a depressed scar over the frontal bone of a seaman. The result up to 3 months postoperatively is successful. On the same day another implant of the preserved tissue was used for the purpose of correcting a saddle nose in a youth with a negative Wassermann reaction. This result also is successful. Tyrode modification (Tobach) is a semi-solid amphoteric material which is both a conductor and a condenser of electrical activity, and has a very high penetration index. It is the ideal preservative for human tissue. Its action is probably due to its electrolytic power, and the latter may be regarded as having the same effect as the blood has in circulation. It is also recommended to be used as a therapeutic measure in cases of inflammatory reaction and disturbed postsurgical blood circulation.

Local implantation of gelatin—Sinclair and Douglas describe experiments in local implantation of gelatin in wounds, based on the conception that "the healing of a wound through fibroplasia might take place more readily if substances needed by the cells surrounding the wound were supplied locally in adequate amounts throughout the entire healing process, rather than if the body were left alone to supply such substances more slowly". Into experimental wounds on the backs of dogs gelatin was implanted. It was observed that irritation or reaction of the tissues was absent and that the gelatin-treated wounds appeared to be drier and to heal with fewer signs of inflammation than did nearby control wounds. Gelatin-implanted wounds had greater tensile strength than had the controls. Ninety per cent of them easily withstood tensions which ruptured control wounds. During the past two years one of the authors has mixed equal parts of gelatin and sulphanilamide with the blood, before it clots, in the wounds inflicted in emergency dental extractions, and has then usually sutured gelatin treated wounds healed faster and looked healthier than did the controls and no ill effects were observed. Treatment of several leg ulcers by dusting them with finely powdered gelatin and then bandaging them in the usual way with Elastoplast, with the adhesive surface directly in contact with the gelatin, appeared to increase rapidly and stability of healing.

Experiments with various substances—Williams and Bissell report on the effects on healing of many substances when applied to uniform-sized wounds in normal rats. Three rats in group (1) were treated with a stated concentration in sesame oil of one of the following: vitamins A, C or D, thiamine hydrochloride (aneurine hydrochloride), nicotinic acid, riboflavin, calcium pantothenate, biotin (vitamin H), pyridoxin, liver extract, or a "vitamin mixture". Two drops of one solution were placed daily on each wound, each rat having 3 wounds of varying depth. Biopsy was done after a varying number of days, depending upon the depth of wound. In group (2) in addition to daily topical application of cod-liver oil or of one of the previously tested substances, the same solution was injected subcutaneously at two edges of each deep wound. The edges were excised after varying intervals. Sterile abscesses which would delay absorption of water soluble substances, several oils and gums were tested. All caused inflammation to some extent. Sesame oil was not used as vehicle in group (4) which was tested with the following additional substances: amino acids, adenosine, hydrolysed gelatin, Biotin, or urea and sulphathiazole ointment. The effect of sulphamethylpyrimidine in conjunction with most of the substances was observed. No notable benefit was derived from the use of any of the substances, as judged by frequent observation of the wounds, their tensile strength and microscopical changes, the extent of epithelialization, mitosis, thickness of the fibrous layer, vascularization and evidence of necrosis or of infection, were especially noted.

Capillary bleeding and fibrin foam—Woodhall considers that the use of fibrin foam, introduced by Ingraham and Bailey, is a most significant advance in the control of capillary bleeding from the substance of the brain or spinal cord, or of haemorrhage in the neighbourhood of living axons which cannot be controlled by use of the silver clip or the electrocautery. He records its use in 226 operations at an American Army neurosurgical centre. Fibrin foam is prepared from human fibrinogen and human thrombin. In actual use, large fragments of fibrin foam are dropped into a previously prepared solution of thrombin in sterile isotonic saline and are then cut according to the particular needs of the operation. The older methods of controlling capillary haemorrhage by cotton patties soaked in warm saline solution and by muscle may cause considerable tissue reaction. Such a reaction was not noted, with fibrin foam. In 2 cases in which re-exploration was required at a later date appearances strongly suggested the beneficial effect of the foam in preventing adherence of nerve roots to adjacent tissues and in preventing the formation of scar tissue from resolving postoperative haematomata. The technical procedures consisted of peripheral nerve neurolysis, neuroorrhaphy and nerve grafting, excision of cerebral scar with tantalum plating of skull defects, hemilaminectomy for rupture of an intervertebral disc, craniotomy for tumour and laminectomy and secured promptly and no untoward reactions to the foam occurred.

Use of absorbable gauze.—Frantz, Clarke and Lattes report on the use of absorbable gauze for the purpose of achieving haemostasis. The gauze used contained 13.5–15.8 per cent carboxyl and had been sterilized with formaldehyde. Experimental lacerated wounds in animals showed that the oxidized gauze was pliable and easy to pack, and when wet with blood, swelled and became sticky, filling all the crevices in the wound and forming a dark brown mass. When this occurred, bleeding ceased. The foreign body thus formed was not incorporated in scar tissue. In serous cavities the use of oxidized gauze resulted in the formation of small cysts which were eventually reabsorbed. After the gauze had been in an open wound for 48 hours, the brown mass formed could be gently scraped away from the wound surface without renewal of bleeding. Experimental wounds, on kidney and spleen principally, were packed with the gauze and the abdominal cavity was closed. Examination of the organs 21–40 days after operation showed that the gauze had largely been absorbed and that many phagocytes were present. Clinical trial was made in 17 cases. In 4 of these packing was imperative and 2 of the wounds were closed which ordinarily would have been left open for withdrawal of packing. In 3 biopsy wounds of liver and sternal marrow the gauze replaced muscle and was considered to be fully as satisfactory. It was used as a convenience in 3 oozing gallbladder beds. In one case which was complicated by a haematoma and pleurisy with effusion, a sympathectomy haemostasis was not secured, and it is suggested that the gauze should have been held in place by suture since there was a great deal of bleeding.

Uses of serum albumin, gamma globulin, fibrinogen and thrombin.—Janeway, in the first of two papers on the clinical uses of the products of human plasma fractionation, discusses the uses of concentrated human serum albumin and gamma globulin. Concentrated human serum albumin is stable and easily transportable. The immediate effects of intravenous injection of it is an increase in the serum albumin concentration resulting in transfer of fluid from the extravascular spaces to the vascular compartment. Its administration to patients in a condition of shock results in an increase of blood volume and haemodilution with clinical improvement. Theoretically, 1 gramme of albumin should hold 18 cubic centimetres of fluid in the circulation and this is borne out by actual clinical experience; thus 25 grammes of albumin is osmotically equivalent to 500 cubic centimetres of citrated plasma. In severe dehydration the injection of albumin must be supplemented by fluids, which can be given orally if tolerated or by other routes. It can be used to correct conditions of hypoproteinaemia. In nephrosis the use of albumin has provided irregular results and further study is required. In the case of γ -globulin it has been shown that the fraction is a safe and effective agent for the prevention and modification of measles. The injection is usually given on the fifth day after exposure. The dosage for complete protection is 0.1–0.075 cubic centimetre per pound body weight or, if modification is desired, 0.025–0.02 cubic centimetre per pound. Reactions were noted in only 1.7 per cent of 1,843 intramuscular injections. In paediatric wards γ -globulin has been shown to be effective in the control of measles outbreaks. In the second paper, Ingraham and Bailey discuss the use of fibrinogen and thrombin in surgery. Fibrin foam—which has a honeycomb structure composed of fibrin with air spaces of varying sizes—when soaked in thrombin solution has been used as a haemostatic agent. It can be left *in situ*, is readily absorbed, and excites minimal tissue reaction. The authors have used this material in 169 neurosurgical operations and they have found that it will control bleeding from the dural sinuses and veins, and oozing from cerebral tissues; its use in arterial bleeding is not advisable. Fibrin foam with thrombin has been experimentally applied in general surgery and has been found to be valuable. It is effective in controlling bleeding in haemophilics. The authors report on the use of a fibrin film which they have employed very successfully in the repair of the dura mater and in the prevention of meningocerebral adhesions, but they are guarded in its evaluation owing to the possibility of the late appearance of reactions so far unrecorded. Further experiments are needed to assess the application of fibrin foam in other sites in surgery.

Alpha rays.—Uhlmann discusses α rays in the treatment of wounds. Radon, a gaseous disintegration product of radium, combines easily with fat and consequently can be used in a form which will permit the utilization of the α rays. These rays form over 90 per cent of radium emanation, but have been little used because their pathway and penetrating power is so limited as to appear to be of no use in the treatment of neoplasms. If they are brought into contact with lesions on the body surface in a radon ointment, however, they appear to have a distinct therapeutic value. The ointment must be freshly made in order to determine the exact concentration, since radon is unstable and half the concentration of a known amount will be lost in about 4 days. It must be kept in airtight containers and applied under airtight dressings so as to prevent any escape of the gas. The number of treatments required varies with each wound. The ointment was used by Uhlmann at first only for wounds resistant to any other form of therapy, particularly for those which occurred after overdoses of radium or of x-rays. When it was found that a new capillary circulation was formed at the site of the disease the ointment was used for other wounds with deficient circulation such as varicose ulcers, electrical burns and fistulae after extensive operations. Uhlmann quotes in detail 8 cases with varying lesions all of which responded well to the treatment and notes not only that the treatment is easy to carry out, but also that the rate of healing is greatly accelerated and the resultant scarring soft and smooth with no impairment to the function of the underlying musculature.

Penicillin in infections of soft tissues—In a critical survey of their experiences with penicillin, Lockwood, White and Murphy review 440 cases. They are concerned chiefly with defining the use of penicillin in surgical infections in soft tissues, bones and serous cavities. Their patients had usually failed to respond to initial sulphonamide treatment. The authors state that when administered systematically penicillin modifies the course of most infections in which the causative organism is sensitive to the drug *in vitro*. When sepsis is disseminated and the circulation in the local lesions is adequate for contact between drug and bacteria to be made, the response is often dramatic. In cases in this group in which surgical treatment would have once seemed to be inevitable, it now often can be postponed or avoided altogether. Failures occurred when an insensitive infecting organism was being dealt with or a case in which the penicillin could not reach the infected area because of poor circulation. The authors stress the need for careful investigations to determine whether or not there are present penicillin-resistant or susceptible organisms such as *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) or *Bacillus proteus* (*Proteus vulgaris*), which elaborate a penicillin destroying substance. In acute disseminated sepsis Lockwood, White and Murphy report a two thirds survival rate in 57 cases of staphylococcal bacteraemia, treated usually by continuous intravenous drip and mostly without resort to surgical treatment. Nineteen cases of empyema due to penicillin-sensitive pneumococci, staphylococci or streptococci were cured by aspiration and by local injection of the drug. Similar results were obtained in suppurative arthritis and very good results in cellulitis of the face and orbit, which are well vascularized areas. Penicillin will regularly control the invasion features of acute osteomyelitis but will rarely, if ever, permit permanent avoidance of surgical intervention. In chronic osteomyelitis penicillin brings about marked reduction of organisms in the exudates of chronic sinuses but surgical removal of infected tissue and bone is required with local penicillin treatment as an adjuvant. The authors consider that there is not any justification for modifying the indications for surgical intervention in cases of appendicitis, cholecystitis and peritonitis. With regard to local penicillin treatment, they stress that the subject needs much further study and that in all localized infections the correlation with surgical interference is not yet sufficiently defined.

Sulphonamide treatment of peripheral nerve wounds—Davis Perret and Carroll describe the effect of the sulphonamides on experimental gunshot wounds of peripheral nerves, and, with Hiller, study the effect of sulphonamides on their regeneration. The wounds were produced at short range by .22 calibre long rifle lead tipped bullets with countersunk or coned out tips and with a muzzle velocity of 1,070 feet per second. The majority of the animals used were cats and the sciatic was the nerve involved. In each case a small round entrance wound was caused and there was a larger irregular ragged wound of exit. Debridement of the wound with simultaneous repair of the nerve was performed immediately, or at various intervals up to 48 hours after injury. It was found that when surgical treatment was begun immediately after injury, infection of wounds was reduced from 38.2 per cent to 5 per cent, and at 6 hours after injury from 42.9 per cent to 10 per cent when sulphonamides were applied locally. The incidence of infection was also considerably lowered by application of sulphonamides to wounds debrided 12–24 hours after injury. If sulphathiazole jelly was introduced into the bullet track at the time of injury, with surgical and local sulphonamide treatment 24–48 hours after, the incidence of infection fell from 83.3 to 22.5 per cent. The use of sulphonamides produced increased adhesions especially about the grafts, when used, and particularly in the case of homogenous grafts. There was an increased mesodermal proliferation at the suture line with reaction. There was no conclusive evidence that regeneration of nerve fibres and the repair process generally were affected adversely by sulphonamides, and they did not interfere with animals in the homogenous graft series which were treated with sulphonamides a heteromorphous neurotization of the graft was found, whereas in untreated animals similar grafts showed some degree of isomorphous neurotization.

Technique of plastic surgery—Kilner discusses the principles concerned in repair work and the importance of avoiding disfiguring scars by directing adequate attention to the original wound. Careful cleansing and haemostasis are required before closure of wounds in which there is no skin loss. Effective suture materials include fine varieties of silk or of nylon or ophthalmic silk, worm gut mounted on eyeless needles. Skin sutures are inserted at right angles within a millimetre of the margin and with 4-inch spacing. Insertion of a subcutaneous wire suture is designed to avoid gaping of facial wounds in which scars cross the expression lines. Skin loss should be made good with the thinnest variety of Thiersch graft. The inner side of the upper arm and the anterior or upper postero-external surface of the thigh are suitable donor areas for hairless grafts. The Wolfe graft is composed of the full thickness of the skin down to but not including fat. If it is taken from hair-bearing skin it forms a satisfactory replacement for a lost eyebrow. Careful repair in layers is necessary for wounds of lining and covering as in the eyelid, nostril and lip. In order to avoid the distortion produced by dragging the parts together it is wiser to take the preliminary step of sewing lining to skin around the margins of extensive facial defects. Replacement of displaced fragments into correct positions must be done before repair work is undertaken in cases of fractures of the facial bones. Mandibular bone loss should be replaced by iliac bone graft in block or chip form. Cartilage, preferably parboiled and cut into small pieces, affords satisfactory material.

Transplantation of whole limbs.—Hall considers that successful transplant of whole limbs in man is now possible, and suggests plans of procedure and operative technique. Infection can be controlled by administration of sulphonamides and of antibacterial agents of the penicillin group. Thrombosis can be prevented by the barium salt of heparin given parenterally and by dicoumarin given orally; the latter has a latent period of 48–72 hours. Complete control of bony fragments, including alignment and fixation, can be obtained by means of the light-weight Stader splint, which consists of a metal bar with at each end a steel pin for insertion into the bone on each side of the fracture; the bar bridges the fracture, the ends of which are drawn together by adjustable screws. The site for choice in the case of the arm appears to be the junction of the middle and lower thirds. The flap incisions in both donor and recipient are so made as to correspond on union. In the donor the longer superficial and deep veins are attached to cannulae leading to a dependent reservoir, so that thereby blood may perfuse the extremity continuously. The biceps tendon is severed with a Z-shaped cut. The median, radial and ulnar nerves are cut, and the ends are sutured to the skin in order to prevent twisting. The brachial artery and veins are severed as proximally as possible, and the artery should be cannulated to a heparinized transfusion through which oxygen is bubbling, and which contains the chosen antibacterial agent. The Stader lower half pin-unit is fixed through the aponeurosis of the biceps which, together with the remaining muscles, is severed. The end of the bone after severance is fashioned into a three-sided blunt point. In the case of the recipient the technical principles are mainly the same as in the case of the donor, but the upper pin-unit is applied first, and brachial artery and deep veins are clamped before severance. One vein may be cannulized for transfusion. The end of the bone is prepared and the graft is joined and aligned, the cannulae having been cut from it. The blood vessels are anastomosed and the epineural sheaths of the nerves are joined. The patient is treated with heparin until the action of dicoumarin is sufficiently effective.

Plasma-thrombin methods.—Young and Favata describe the suture of wounds by plasma-thrombin fixation. Describing the method of plasma-thrombin suture they state that they believe the use of autologous plasma to be unnecessary. They use stock pooled plasma with which the wound is thoroughly moistened, excess being avoided. A solution of thrombin in sterile isotonic sodium chloride is sprayed on the wound with a syringe and needle, the strength of the solution depending upon the desired rapidity of clotting. The authors have found that if 250 units of thrombin are dissolved in 10 cubic centimetres of saline solution, 1 part will clot 4 parts of plasma *in vitro* in 35 seconds. The wound edges are adjusted and held in position for about 2 minutes or for twice as long as it takes fibrin to form with the strength of solution used. In 18 cases of lacerations, using this method with a thrombin solution of 250 units in 5 cubic centimetres, healing has taken place without infection and has resulted in a final scar as good as if not better than would have been the case if stitches had been used. In 8 cases of elective operations on the face and neck in which a good scar was particularly desirable, the method in all cases obtained primary healing with hairline scars. The authors have also used the method in cases of radical mastectomy in an attempt to avoid the postoperative complication of fluid collections under the wound flaps. Of 10 cases there was not any fluid in 8 and in 2 fluid had to be subsequently aspirated. Describing their

experiences with this method in skin grafting, Young and Favata consider that it has a definite usefulness as an adjunct to the usual method of fixation. They consider that adherence of scars and wound flaps can be readily obtained and that since the tensile strength in this method is not as great as in ordinary suture methods, its use should be limited to cases in which tension is not present.

Wartime wounds—Romanis describes the pathological methods involved in the repair and healing of cuts and wounds. Healing by first intention is quick but the process is considerably delayed when the surface of the wound is covered by granulations or pus. In clean granulating wounds, however, final healing may occasionally be hastened by drawing the edges together with loose sutures. Gunshot wounds encountered in wartime are more serious problems for the surgeon than are the cuts and wounds of civil practice. Treatment of shock must take precedence over repair of injuries, and haemorrhage needs urgent attention especially after large arteries have been cut by flying glass. Minor cuts should be washed with running water and cleansed with antiseptic solution before the insertion of sutures. A limited amount of excision of damaged parts may be required for extensive lacerations but care should be taken to search for lesions of structures such as nerves or tendons. Primary suture of these tissues is of considerable value. Excision is required for gunshot wounds which are treated within 12 hours of the incident but not for clean through-and-through bullet wounds. Patients with infected wounds of over 12 hours' duration should receive expectant treatment after obvious pieces of dirt and foreign bodies have been removed. These wounds must be watched for evidence of spreading infection or gas gangrene. Secondary haemorrhage may occur when sepsis has been present for 10 days or more and the bleeding point must be found and tied. It may be necessary to tie the main vessel some distance away from the wound. Blood transfusion increases the powers of resistance, and sulphonamides and penicillin combat infection. Skin grafting is employed when the wound has become covered by clean granulations and, with the advent of sound healing, the patient should attend a rehabilitation clinic.

Head and face

Addition of pigments to facial skin-flaps—Full thickness skin grafts from behind the ear or forehead flaps used to reconstruct facial features usually result in reasonably good colour matches with face skin. With grafts and flaps from other areas there is often a colour contrast which detracts from an otherwise good result and Hance and her associates describe a method of introducing permanent pigments into the transplanted skin in order to overcome this defect. Such pigments must be non-poisonous, stable to light and non-irritating to the skin and stable to the prolonged effect of tissue metabolism. Among the pigments used are barium sulphate, ochres mixed with clay, chalk or gypsum, carbon and alizarin. The dry colours are mixed and made into a cream with saline and are injected on needle points into the sterilized skin. There is a period of inflammation after injection which lasts for about a week and is followed by desquamation. Second treatments are often needed in order to secure adequate matching. Hard scarring interferes with the process and the most suitable areas are those without pigmentation or with soft white scars. Skin grafts should be old enough to have relaxed before the treatment is given. The colour of skin flaps is more likely to be dead white or yellowish than too dark, the texture is better and there is less superficial scarring than in the free graft. Pigment injection may therefore be done more easily. The method has been used successfully to simulate missing vermillion of the lip. There have not been any complications from the procedure.

Ophthalmology of war surgery—Rycroft reports on methods evolved by army ophthalmologists for the purpose of controlling deep intra-ocular infection due to penetrating wounds sustained in battle. Prophylactic measures are summarized as (1) the issue of Perspex anti-devastating blast effect and produce a multitude of wounds with non-magnetizable foreign bodies, (2) simple cleansing measures for eye wounds to be taken by general surgeons in forward areas, (3) early magnet application and removal of intra-ocular foreign bodies from entry wounds, excision of prolapses and closure of wounds by skilled ophthalmic surgeons working as far forward as possible, (4) routine insufflation of penicillin powder into every ocular wound for the purpose of sterilizing the conjunctiva. After evacuation by air to a base and are removed surgically. Routine sulphonamide therapy for septic cases and non-specific protein shock in cases of hypopyon and iritis are valuable. Certain corneal lesions resulting from Schu mine injuries benefit from Saemisch section. Penicillin is of proved value for superficial eye infections. Experiments to test its effectiveness in deep intra-ocular infections are described. Penicillin assay was done on the media of normal eyes removed soon after death from casualties who had received large doses of penicillin by the intramuscular route when moribund, and on those of traumatized eyes immediately after enucleation. The results appeared to show that penicillin given intramuscularly does not enter the ocular media, nor is the course of deep intra-ocular infection influenced. The local effect of penicillin injected directly into the aqueous and vitreous humours of infected eyes was then investigated. Results in 7 cases showed that, although the eye will tolerate and retain large concentrations of penicillin injected into the media, deep infection is not controlled thereby. The value of penicillin in the control of deep intra-ocular infection lies in prevention rather than in cure. Penicillin should therefore be applied locally as soon as possible after the eye has been wounded.

Tantalum in the closure of skull defects.—Gardner stresses the importance of closing defects of the skull, for which he advocates the use of tantalum. Tantalum is a biologically inert pure metal which, in a thickness of 0.3 millimetre, affords adequate protection over a cranial defect of any size and is sufficiently malleable to be cut and shaped at the operation table with ordinary tin shears and a hammer. The implant should be fastened to the skull with small tantalum screws. The author maintains that the closure of skull defects is essential in order to prevent the pulsation which occurs within a trephined skull and to provide the immobilization necessary for wound healing; he quotes the finding of Grant and Norcross that 18 out of 27 patients were relieved of post-traumatic epilepsy by mere repair of cranial defects. He suggests that migration of the cerebral ventricle towards the site of a traumatic skull defect is due not merely to loss of brain tissue and scar contraction but also to progressive gliosis and atrophy of the pulsating portion of brain beneath the skull defect. He reports on 15, in 7 of which there were large unrepaired dural defects beneath the implants. In 5 patients accumulations of cerebrospinal fluid collected between scalp and implant and persisted, without impairing results, for some weeks. Perforation of the implants affected neither occurrence nor duration of fluid collection but a few turns of elastic bandage over the dressing controlled it and the author considers this method preferable to the introduction of any extraneous material as a dural substitute. The accumulation is not the result of irritation but of the lifting of the scalp from the smooth surface of the implant by the cerebrospinal fluid pressure. There was one fatal infection attributed not to the tantalum implant but to operating too soon after scalp infection. In another case, at necropsy 8½ months after operation, there was no evidence of corrosion of the implant or of irritation or proliferation of bone beneath it. Unfortunately tantalum is radio-opaque and also acts as a filter and a secondary radiator.

Trunk

Gunshot wounds of the colon.—Morgan discusses wounds of the colon occurring in soldiers in the Middle East and analyses 128 cases, mostly of survivors. Injuries of the right, transverse and left colon occurred with nearly equal frequency, the caecum and transverse colon being most commonly injured from the front, whereas the fixed portions, the ascending and descending colon and the flexures, were usually damaged from the back. The pelvic colon was injured from below, from the front and from the back. The colon was most often injured by entry wounds in the lower abdominal quadrants. The number of survivors for each segment of the colon was approximately equal, but the survival rate of patients with transverse colon wounds was markedly lower when they were operated on more than 6 hours after being wounded—probably on account of the greater danger of severe haemorrhage and the greater frequency of involvement of other organs. As regards treatment of the injured colon, exteriorization of the damaged portion is the safest procedure, or in urgent cases with a short loop the injured colon may be sutured to the parietal peritoneum. The next best method is closure of the perforation with two layers of sutures, and its complete exclusion by a proximal colostomy. The main essentials of postoperative care are continuous intravenous therapy, decompression of the gastro-intestinal tract by suction through a duodenal tube, and administration of morphine. Patients should be evacuated until normal gastro-intestinal activity is restored and there is cardiovascular stability and a satisfactory fluid and salt balance. The average time before evacuation was 13.5 days. Sulphonamides are undoubtedly of value; 10 grammes of sulphadiazine suspension were placed in the peritoneal cavity after operation. Complications after operation were haemorrhage, peritonitis, pneumonia, pelvic and retro-peritoneal abscess and intestinal obstruction. Three patients with multiple colon wounds survived exteriorization of the injured portions. Colectomy was performed twice for extensive tearing of ascending and descending colon, but both patients died.

Disruption of wounds and ascorbic acid and protein deficiencies.—Kraybill describes 7 cases of total disruption of wounds occurring in 375 abdominal sections, an incidence which agrees with other recorded series. The nature of the primary disease, the site of incision, inadequate closure of the posterior rectus sheath and the nature and absorbability of suture material have all been held by different observers to be responsible for this complication. Kraybill discusses in particular the possible relationship of hypoproteinaemia and deficiency of plasma ascorbic acid. In none of these 7 cases was there detectable ascorbic acid in the plasma at the time of total disruption. In 5 cases the administration of 150 milligrams of ascorbic acid daily failed to produce a detectable plasma content in a week and not until after 6 weeks on this dosage was it noted in one patient. Experiments of Lund and Bartlett have shown the necessity for adequate amounts of ascorbic acid in order to maintain tensile strength in healing wounds and the deposition of collagen, but it is likely that longstanding deficiency in vitamin C exists before wound healing is adversely affected. Big doses of ascorbic acid are essential in treatment. Consistently low plasma protein levels were recorded in 6 of the cases. Hypoproteinaemia may be acute—as in cases of haemorrhage, burns and intestinal obstruction—or chronic, from nutritional causes. Its diagnosis value may be masked by dehydration. In Kraybill's series the general condition of the patients paralleled very closely the level of their plasma proteins. The average time of disruption was 9 days after operation.

Limbs

Repair of blood vessels.—Blakemore and Lord recommend a routine treatment for wounded extremities with main artery damage. Immediate control of haemorrhage, by tourniquet if necessary, is succeeded by whole blood transfusions for the purpose of combating shock and

Excision of tissue should be avoided if possible. The commonest bony injury is fracture and displacement of the nasal bones and septum to one side and these can be restored by digital pressure. A direct blow may cause backward impaction of the nasal bones into the ethmoid area. The bones must be disimpacted and the fragments moulded into their correct position, re-impaction being prevented if necessary by suturing the nose to a rubber or lead splint lying along its surface. If the force of the blow is oblique, the malar zygomatic region may be depressed backwards and downwards. This can be corrected by an elevator pressed deep to the temporal fascia if the bone is not fragmented, but if there is a comminuted fracture there will be great oedema of the soft tissues, making estimation of the extent of damage difficult. Routine x-ray views are not helpful, but a 30° or 50° occipito-mental view has diagnostic value. The fragments must be moulded into position through a sinusal opening, as for a Caldwell-Luc operation, and the antrum then packed for 14 days in order to allow for fibrous union. Mowlem concludes by emphasizing the need for prompt treatment so as to prevent permanent disability.

Investigation of sequelae.—Ross and McNaughton describe the results of an inquiry into the post-traumatic complaints of 90 subjects who had suffered head injuries several months or more previously. Sixty-eight patients, military and civil, came for treatment of various disabilities—headache, dizziness, fatigue, irritability and impaired efficiency; 22 who had no complaints submitted themselves to investigation as controls, at the request of the inquirers. The data collected consisted of types of headache, previous personality background, severity of injury, electroencephalographic and pneumoencephalographic reports, "instability" and "disability" as determined by the Rorschach method and certain situational factors. Every head injury involves physical and psychic trauma. Patients with localized headache showed more evidence of cerebral damage and less evidence of previous neurotic background. Meningeal contusions and adhesions may be directly responsible for the headache, which may spontaneously cease in time or may require operative measures; persistent headache may have an emotional basis. Many of the findings showed a psychoneurotic pattern in the later stages. For example, the Rorschach ratings, in cases of severe injury, may pass from "disability" to "instability", to become normal on recovery. Patients with bizarre, generalized and bilateral headaches appear to approach a hysterical condition, those with the occipital form showing anxiety and tension. Patients without headache but with other symptoms such as dizziness and fainting fits, were found to have previously unstable personality; the same applied also to the controls. Physiogenic and psychogenic factors cannot be completely dissociated in the living person, and the patient and his setting must be considered as a whole.

Trunk

Possibility of intestinal rupture.—Hunt and Bowden discuss intestinal rupture caused by relatively minor non-penetrating trauma of the abdominal wall. They describe in detail 6 cases, 2 of which were complicated by other injuries; it is emphasized that the latter may mask the intra-abdominal lesion, at any rate on preliminary examination; early diagnosis is essential, for if treatment is delayed for 12 hours, mortality may be 70 per cent, as in 17 cases reported on by Poer and Woliver. In 14 of these authors' cases, in which early diagnosis and prompt treatment occurred, mortality was 35 per cent. Great caution in diagnosis is essential in apparently trivial abdominal injuries since the appearance of symptoms may be delayed owing (1) to incomplete intestinal rupture; (2) to intestinal paresis, followed by leakage when later peristaltic action is resumed, in the manner described by Cope; (3) to prevention of leakage mechanically by plugging by mucosal layers or by contraction of musculature of divided ends in a complete transverse division. Continued vomiting on recovery from shock, rigidity and rectal tenderness due to gravitation into the pelvis of irritating intestinal contents, are all very valuable signs. Cope advocates laparotomy if, in the absence of thoracic or renal injury, there are present severe abdominal pain persisting for 6 hours, vomiting, gradually rising pulse, local rigidity and deep local tenderness or if there is a steadily rising pulse rate, especially if the patient is restless and listless. Hunt and Bowden emphasize the possibility of intestinal perforation after even minor trauma of the abdominal wall, and the importance of prompt laparotomy at the first sign of peritonitis.

General

Nerves

Autologous plasma clot and tantalum in peripheral nerve suture.—Although the condition of nerve stumps and of muscles and end-organs innervated by the nerve are of paramount importance to the outcome of nerve suture, the technique of suture is also important. Tarlov reports on encouraging results from the technique of peripheral nerve suture using autologous plasma clot in combination with tantalum wire tension sutures. This seems to allow better apposition of nerve ends with less disorganization at the suture site than are obtained with any type of thread apposition suture. In 7 of the 14 patients treated, sufficient time has elapsed since operation to justify some conclusions being drawn about the procedure. One woman whose spinal accessory nerve was sutured one hour after severance at operation showed complete functional recovery of the sternomastoid muscle 5½ months later. Another patient, 15 months after traumatic severance of his ulnar nerve at wrist level, had nerve stumps 2 centimetres apart at the time of operation. Now, 18 months later, he shows good recovery of sensory and motor functions of the hand and clear diminution of the muscle atrophy. Thirdly, satisfactory sensory but very little motor recovery occurred after excision of a neuroma in

The systolic pressure may be abnormally high without causing anxiety, provided that the diastolic pressure is below 90 millimetres of mercury. Premature systoles are common in otherwise normal adults, especially in heavy smokers. A mild degree of atrial fibrillation is compatible with a normal life, but no insurance company will accept this risk. In cases of valvular disease the condition of the heart muscle is all-important in weighing prospects of life. The urine should be tested for albumin and sugar. A little albumin, of non-renal origin, may be found in the urine of elderly men with slight catarrh of the prostate or bladder. No pathological significance need be attached to orthostatic albuminuria or to the transitory glycosuria associated with a meal rich in carbohydrates. Fehling's test is satisfactory but the use of Benedict's solution avoids false reactions.

Brockbank, E. M. (1944) *Med. Pr.*, 212, 280.

INTESTINAL OBSTRUCTION

See also B.E.M.P., Vol. VII, p. 221; and Cumulative Supplement, Nos. 761-775.

Acute intestinal obstruction

Chief types of intestinal obstruction

Chronic intussusception observed by skiagrams.—Hellmer describes a case of chronic intussusception with spontaneous reduction in which the process was followed by means of successive skiagrams; it was the only such case encountered by him in a series of 128 cases of intussusception in which a radiological diagnosis was made. The patient, a female infant aged 19 months, was admitted to hospital on the third day of illness, which had begun with an attack of colic followed next day by the passage of a bloody stool. The pain recurred on the day of admission. The only abnormality detected on examination was resistance below the right costal margin. A barium enema showed the apex of the intussusception to be in the ascending colon, and when the pressure of fluid was increased by raising the receptacle the apex was seen to move proximally. The pressure was further increased and with the aid of manual pressure the intussusception was completely reduced and the barium could be seen to enter the small intestine. The child was discharged from hospital, but continued to have attacks of pain and was readmitted after 6 days. X-ray examination showed the intussusception to have recurred; attempts at reduction by running in barium were unsuccessful. The child did not appear to be ill and a waiting policy was adopted; 8 days afterwards, since no symptoms were present, she was discharged from hospital. For one year she was symptom free, and was then readmitted to hospital with acute attacks of abdominal pain recurring every 5-10 minutes; further x-ray films were made and the contrast medium was shown to run through unobstructed. The author considers that spontaneous reduction took place at about the same time as the x-ray examination was made. The child has remained free from any symptoms for 6 years. Hellmer suggests that similar cases may not be rare, and will go undiagnosed unless they are investigated radiologically.

Effect of gallstones.—Acute intestinal obstruction by gallstones, although rare, has the highest mortality of all obstructions. Lee states that many cases show no previous history of gallbladder trouble. Cases mostly occur in old people and pre-operative diagnosis of the cause of the obstruction is unusual. Remissions and recurrence of obstruction are common, due to moving of the stone, which is always large and enters the bowel primarily by a fistulous communication, usually between the gallbladder and duodenum. In most cases the stone is found ultimately in the terminal ileum. In diagnosis, suspicion must be attached to any history of abdominal pain and vomiting lasting for over 24 hours and increased borborygmi associated with pain, both pieces of evidence suggesting obstruction. Stethoscopic examination of the abdomen is of great importance. Radiographic examination sometimes shows the outline of a stone in the intestine. Early operation is indicated, without a general anaesthetic because of the excessive vomiting, and Lee favours direct incision of the intestine over the stone on account of the spastic ileus which usually prevents any milking of the stone to another site. The possibility of crushing the stone *in situ* by introducing forceps into the lumen offers an alternative procedure. Lee records a case in a woman of 87 years of age, from whom a stone the size of a walnut was removed under spinal anaesthesia from the lower ileum. Three months later a second obstruction occurred and a stone as big as a golf ball was found in the ileum.

Chronic intestinal obstruction

Clinical picture

Argentaffin tumour of the ileum.—Ritchie and Stafford report on a case in which an argentaffin tumour developed in the ileum. The patient, a woman aged 58 years, complained of loss of weight, abdominal pain and diarrhoea. Chemical tests showed the presence of blood in the stools, an abnormality which was subsequently attributed to vascular occlusion and to necrosis in the region of the primary growth. The liver was enlarged and this enlargement was considered to be due to carcinomatous metastases, although the primary site was undetermined until the patient died. At necropsy a neoplasm was found in the ileum, near the ileo-caecal valve. There were many abdominal metastases and the entire right lobe of the liver was filled with masses of neoplastic tissue containing blood and necrotic material. Microscopical examination showed a primary argentaffin tumour of the ileum with secondary abdominal growths. The deposits in the spleen had not been seen macroscopically. The authors

state that 332 cases of argentaffin tumour have been reported on and that the incidence of metastasis is 37.9 per cent. In only three cases however have haematogenous metastases been found in the spleen. Partial or complete obstruction of the small bowel occurs in many instances and this condition may be confirmed by radiographic examination. Diarrhoea is of no diagnostic value unless the stools are found to contain blood. It is proposed that the term carcinoid should be discarded. A tumour with cancerous properties is described as argentaffin carcinoma but otherwise the growth is termed benign argentaffin tumour.

Hellmer H (1944) *Acta radiol Stockh* 25 514

Lee M (1945) *Brit med J* 1 555

Ritchie G and Stafford W T (1944) *Arch Path* 38 123

JOINTS, DISEASES AND DISORDERS

See also B E M P Vol VII p 278

Tumours of the synovial membrane

Neoplasm

Synovial sarcoma—Haagensen and Stout discuss synovial sarcoma. After tissue culture studies of 3 cases the authors have concluded that the histological characteristics of these tumours are an inextricable mixture of mesothelial cells secreting a mucicarmophilic substance and strands of active hyperchromatic fibrosarcoma like cells the relative proportions varying from case to case. Using these findings as a criterion Haagensen and Stout have collected 95 cases from the literature and report on 9 previously unrecorded cases. The mean age of the patients was 32 years. Nearly half the number of tumours were in the region of the knee joint. The initial symptom is pain and in 25 per cent there was a history of trauma. The mean duration of the symptoms before treatment was 2.6 years in the 98 cases in which the information was available. The total mean duration of the disease was 5.7 years among 42 patients who have died. Although the disease remains localized for a number of years metastases usually appear the blood stream is the usual route but occasionally metastases are carried via the lymphatic vessels to the lymphatic glands. The tumours usually start from a focal point and grow by expansion, so that they are circumscribed as they infiltrate they become more or less adherent to surrounding structures. Histologically the formation of the mucicarmophilic substance differentiates them from haemangio endotheliomata and chorionepitheliomata. In the present series of cases only 3 patients are reported to be clinically cured over a 5 year period. Discussing the method of treatment and results the authors advocate incisional biopsy and then a high radical amputation as offering the best chance for the patient. Since the diagnosis rests to a considerable extent on the recognition of the histological architecture of the lesion aspiration biopsy is not advisable. Because of the number of instances of metastasis in the regional lymph glands the authors suggest that subsequent dissection of these should be considered.

Hip joint

General

Arthroplasty—Bickel, Ghormley, Coventry and Mussey present results of cup arthroplasty of the hip performed 111 times in 91 patients. Follow up data were obtained in 88 cases after postoperative periods varying from 8 months to 5 years. Results were classified as very good, good, fair and poor according to the presence or absence of pain and limp and the degree of improvement of motion of the limb. The 91 cases in 20 of which bilateral cup arthroplasty was performed included 28 cases of osteoarthritis, 12 cases of rheumatoid arthritis and 19 cases of rheumatoid spondylitis. The most uniformly disappointing results were obtained in 7 cases of aseptic necrosis of the femoral head. Results were better among men than among women. The percentage of very good and good results was greater among cases in which operation was performed on one hip than in those in which both hips were subjected to operation. Study of postoperative roentgenographic findings showed no clear causes for proliferative changes or in retrospect the selection of patients later considered to be poor subjects because of certain anatomical features of pelvis and femoral necks or heads. The use of a vitallium cup gave a greater percentage of very good and good results than did the use of a Lucite (a translucent resin) cup. The authors consider that these results although not uniformly satisfactory are sufficiently encouraging to justify the use of the procedure. Better operative technique and selection of patients may improve results.

Bickel W H, Ghormley R K, Coventry M B and Mussey R D Jun
(1944) *Proc Mayo Clin* 19 561
Haagensen C D., and Stout A P (1944) *Ann Surg* 120 826

See also B E M P Vol VII p 330 and Cumulative Supplement Key No 826

Aetiology

Occurrence in China

Importance of the dog as a reservoir host—Scovel states that kala azar is endemic throughout Northern China and is most prevalent in Hopei, Manchuria, Anhwei and Kiangsu. Kala azar is usually a disease of villages and it follows in the wake of poverty, famine, flood and war. The author saw 185 cases in 18 months and the rate of incidence was highest in patients

KALA-AZAR

below the age of 15 years. It is believed that the disease is transmitted to man by the bites of infected sandflies. This is borne out by the ability of *Phlebotomus chinensis* to receive and retain the parasites. Moreover the flagellates grow in the intestine of the fly and extend forward into the proboscis. The dog is a reservoir host, for it is to be noted that, as shown by similar complement fixation reactions, *Leishmania canis* and *Leishmania donovani* are apparently identical. The most important physical sign in man is an enlarged spleen which usually reaches the umbilicus within 12 months. Blood examination shows an anaemia and a leucopenia. Sternal marrow smears contained Leishman-Donovan bodies in 81 per cent of a series of 557 examinations. It was found that the course of the disease was long, the patients remaining ambulant until some complication supervened. The most common complications were bronchitis, pneumonia, dysentery and noma (cancrum oris). The mortality rate was 5.1 per cent. Prophylaxis included the segregation of patients, the eradication of conditions contributing to the breeding of sandflies and the removal of infected dogs. The patients were treated with pentavalent antimony compounds, and Neostibosan was the drug of choice since it was uniformly effective and reactions were mild or absent. The dose was based on body weight, being approximately 1 gramme for each 33 pounds. From 9 to 16 injections were given intravenously in a solution of 0.5 per cent.

Treatment

Pentavalent compounds

Results of stilbamidine therapy.—Kirk and Henry review the treatment of kala-azar. After the beginning of the recent war, stocks of Neostibosan—a German product which was then the drug of choice—could not be replenished. It was anticipated that outbreaks of kala-azar would occur in East Africa, and supplies of stilbamidine were obtained. The immediate and late toxic effects of this substance are described by the authors. Immediate reactions were lessened by giving injections slowly while the patient was in bed. Relapses occurred, and investigations showed that the late toxic reactions were due to chemical changes in old solutions, accelerated by exposure to light. The drug is eliminated by the kidneys. After the sixth injection of 50 milligrams, given on alternate days, much greater elimination took place, indicating that adsorption on the tissues was complete. Toxic effects were not due to cumulative action. Freshly made solutions had no ill effects. In order to save space in aircraft, 1-gramme ampoules were sent, and before use were dissolved in 100 cubic centimetres of distilled water placed in a rubber-capped bottle. Even small doses of the bottled solution may produce severe toxic effects. Yorke showed that the increase in toxicity is due to exposure to light, that trypanocidal action is reduced and that only unsaturated compounds exhibit these changes. There is some evidence that further chemical changes may develop in old solutions, these diminishing the previously augmented toxicity. Kirk and Henry recommend that only freshly made solutions be used immediately they are prepared. The authors offer no positive opinion concerning the causation of the pathological changes seen chiefly in the kidneys and the liver.

Kirk, R., and Henry, A. J. (1944) *Ann. trop. Med. Parasit.*, 38, 99.

Scovel, F. G. (1944) *Ann. intern. Med.*, 21, 607.

KETOSIS

See also B.E.M.P., Vol. VII, p. 372.

Aetiology

Ketone bodies

General review of ketosis.—Soskin and Levine discuss the method of production and the treatment of ketosis. They consider that the “ β -oxidation-acetic acid condensation hypothesis” of McKay and his co-workers—briefly, that ketones are formed by the condensation of two acetic acid molecules—offers the most reasonable explanation of the known facts. The authors describe experiments and give data to show that for practical purposes the liver may be regarded as the chief if not the only source of ketone bodies in the intact organism, in which the regulation of these substances depends upon factors which either increase or decrease the rate of their formation by the hepatic cells. The scarcity of information about the endocrine regulation of ketone bodies is emphasized but evidence is cited to show that insulin is antiketogenic, whereas the anterior lobe of the hypophysis and the suprarenal cortex are ketogenic. Soskin and Levine think that ketone bodies are probably normal intermediaries of fatty acid catabolism in the liver, which appear in excess in the blood when the hepatic metabolism of fat occurs at a sufficient speed either by lack of or disturbance of the normal regulation of carbohydrate substrate. Causes of ketosis are listed as follows: starvation, high fat diet, excessive vomiting, alkalosis, fever and infective diseases, anaesthesia, hepatitis and early cirrhosis, advanced circulatory failure, glycogen disease, diabetes mellitus, acromegaly, suprarenal cortical hyperfunction, hyperthyroidism, pregnancy and menstruation, and violent exercise. The secondary effects of ketosis, and the resulting tissue pathology, the authors summarize as dehydration, haemoconcentration and cerebral anoxia. They emphasize that the essential treatment of diabetes is the “early, adequate and persistent administration of insulin”, which will be rendered more effective by the simultaneous giving of adequate amounts of carbohydrate, water and salt. Soskin and Levine stress that in non-diabetic ketosis the administration of insulin “can do no good and may do harm”.

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KALA-AZAR

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second stage, voluntary effort appeared to be most important, especially in multiparae with weak pains. The character of the labour pains was on an average a 20-minute, largeness of the baby a 6-minute and unruptured membranes a 3-minute factor. Occiput posterior, late internal rotation and incomplete flexion were negligible factors, unless combined with other adverse factors. Failure of descent occurred only twice in this series, which included no abnormal presentations although in some cases unusual conditions were present. Calkins concludes that apparent failure or delay in descent is almost always due to an incompletely dilated cervix. Vaginal examination then will reveal a rim of cervix still holding the head at a high station, and therefore the second stage has not begun.

Conduct of normal labour

Antisepsis and asepsis

Value of Bimerphen as vaginal antiseptic.—Gates compares the value of Bimerphen with that of other antiseptics for vaginal instillation prior to delivery. His criteria are safety to mother and child, germicidal and bacteriostatic properties, rapidity of action, ease of application, absence of staining, ready availability and economy. Bimerphen is a combination of hexyl *m*-cresol 1 in 1,000 and phenylmercuric acetate 1 in 1,000 in 75 per cent propylene glycol. This combination is distinctly bacteriostatic and bactericidal, is effective in presence of serum and other body fluids and is non-staining. Half a fluid ounce of Bimerphen solution was instilled into the vagina with a special sterile syringe and was repeated 4-hourly until delivery. Most primiparae received 3 doses and multiparae one dose. The respective morbidities were 5.38 per cent and 5.53 per cent, although the operative incidence was respectively 5.3 per cent and 0.5 per cent, morbidity being based on two or more temperatures of 100.4° F. or more occurring during the puerperium after the first 24 hours. Total morbidity percentage after use of Bimerphen was 6.70, a little more than half that experienced after use of other antiseptics. The author concludes, however, that the choice of antiseptic is less important than is the adoption of vaginal instillation.

Management

Prevention of stillbirth.—Congenital defect, asphyxia, intracranial haemorrhage and prematurity caused 80 per cent of 413 stillbirths and 70 per cent of neonatal deaths in 4 recent years at Simpson Maternity Pavilion, Edinburgh. Sturrock considers that methods of reducing mortality due to the last 3 causes are primarily an obstetrical responsibility, and points out that other countries have successfully reduced the incidence of stillbirths and a proportion of neonatal deaths. Adequate maternal nutrition will diminish the incidence of prematurity, which was a factor in nearly half the number of cases tabulated, may also limit toxæmia and eventually may eliminate contracted pelvis. Asphyxia caused 40 per cent of stillbirths and 30 per cent of neonatal deaths. Of these 285 cases 129 were due to premature placental separation and were therefore largely non-preventable. Theoretically preventable are asphyxia due to obliteration of funic circulation and prolonged labour and anoxaemia during anaesthesia, as well as intracranial haemorrhage which caused death in 44 breech, 45 forceps and 50 spontaneous vertex deliveries. Better practical midwifery, in which judgment and technical skill are equally necessary to deal especially with prolonged labour, should partially reduce mortality in this group. Whereas intracranial haemorrhage may result from premature or unwarranted interference in delayed labour, asphyxia may result from overconservatism. Since the fetal mortality rate increases markedly after 30 hours of labour, unless satisfactory progress continues in the absence of maternal or fetal distress after this duration, suitable operative delivery is justified. As aids in reducing the risk from, or extent of, intracranial haemorrhage in the newborn, the following measures are recommended: (1) Early recognition and suitable treatment of cord prolapse; (2) employment of anaesthesia when uterine action is excessive; (3) episiotomy when indicated in premature births or in inconvertible breech presentations necessitating gentle extraction of the aftercoming head; (4) administration of vitamin K in suspected cases. Artificial respiration in cases of asphyxia neonatorum should be avoided. Warmth and gentle handling are required; the latter is also imperative in cases in which intracranial haemorrhage is suspected.

Two phases of the third stage.—O'Connor considers that contradictory textbook advice regarding conduct of the third stage of labour is partly due to non-recognition of the two distinct phases which occur. First, the placenta separates from the uterine wall immediately at the end of the second stage or within one or two postpartum contractions, according to the evidence cited. No signs accompany this phase. Secondly, delivery of the placenta follows its expulsion into the lower uterine segment or through the cervix, the signs being a rising up of the uterus, descent of the cord and possibly bleeding. Separation may be delayed or its completion hindered by the use of general anaesthetics, but intravenous ergonovine (ergometrine) will usually restore the mechanism to the normal. O'Connor believes that anaesthetized patients will not expel the placenta, and he describes an active routine used by him in 900 cases for the purpose of terminating the third stage of labour in 5-7 minutes. One ampoule of ergonovine is given immediately after delivery of the baby's anterior shoulder. Release of the clamp on the placental end of the cord allows reduction in placental bulk. One hand placed on the fundus of the vigorously contracting uterus then expresses the placenta. Failing delivery, after 1 minute fundal pressure is repeated or, if this is ineffectual, the cord is pulled upon provided the fundus feels hard. Over 90 per cent of the author's cases were delivered thus in 3 or 4 minutes. In 6 per cent, other procedures were required. In about

1 case in 60 manual removal was carried out, justifiably, O'Connor considers, since it was done before the patient had lost blood and before bacterial invasion of the uterus occurred. Material mortality was nil, morbidity insignificant. Phlebitis occurred once, postpartum haemorrhage occurred 8 times but was only twice attributable to conduct of the third stage, and was due to retained placental tissue.

Calkins, L. A. (1944) *Amer J Obstet Gynec*, 48, 798

Gates, R. R. (1944) *Amer J Obstet Gynec*, 48, 246

O'Connor, C. T. (1944) *Amer J Obstet Gynec*, 48, 683

Sturrock, J. (1944) *Edinb med J*, 51, 417

LABOUR: MALPOSITION AND MALPRESENTATION OF THE HEAD

See also B E M P, Vol VII, p 451, and Cumulative Supplement, Key Nos 848-853

Occipito-posterior positions

Diagnosis

Anaesthesia and x rays—Corbet gives an account of the aetiology, diagnosis and management of the occipito posterior presentation. The factors which predispose to this position comprise lack of flexion of the fetal spine and abnormal shapes of the pelvis. These abnormalities include the flat pelvis and the anthropoid type of pelvis in which the true conjugate is as long as, or longer than, the transverse diameter. The presentation is also associated with the pelvis which is narrow anteriorly and roomy posteriorly. On abdominal examination it is found that the lumbi are unduly prominent on one side and that the fetal heart is heard on the opposite side, towards the loin and below the umbilicus. The head often appears to lie high but it is difficult to palpate the back. During labour vaginal examination determines the position of the fontanelles and the fetal ear, but the case sometimes requires deep anaesthesia for this purpose. Investigation by means of x rays may confirm the clinical observations. Caesarean section is usually necessary when the disproportion is due to a contracted pelvis. If the pelvic measurements are normal, however, spontaneous delivery is to be expected after the fetus has rotated anteriorly. In some cases the head may become arrested in the posterior position. Delivery by forceps is then required, with or without preliminary manual rotation. Should internal rotation fail to occur, manual rotation becomes essential, because forceps applied without this manoeuvre may cause considerable trauma. In these circumstances preparations must be made to treat the complications of a difficult labour.

Corbet, R. M. (1944) *Med Pr*, 212, 278

LABOUR: OPERATIVE AND MANIPULATIVE PROCEDURES

See also B E M P, Vol VII, p 533

Induction of labour

Methods

Rectal tube versus artificial rupture of membranes—Mackie reports the results of a statistical survey on the induction of labour by means of the rectal tube and by artificial rupture of the membranes. The survey was designed to determine which method was the more effective. Pregnancy had advanced to at least 28 weeks in every case considered. There were 278 cases of tubal induction and 393 cases of artificial rupture of the membranes. Seven maternal deaths occurred in the former group but only 2 deaths took place in the latter series of cases. The morbidity rate was greater in patients induced by rectal tube for the cases included 5 severe anaerobic infections with 2 deaths. This increased incidence of anaerobic infection is probably to be explained by the introduction of a foreign body into the uterine cavity through the vagina in which anaerobic organisms are commonly found. As pregnancy approaches term the time from induction to delivery gradually increases after tubal induction, whereas the interval becomes progressively shorter after artificial rupture of the membranes. More-over the latter method is associated with a comparatively low fetal mortality rate. It is concluded that the results of artificial rupture of the membranes are much superior to those of tubal induction.

Caesarean section

Introductory

Choice of operation—Briscoe discusses the relation of the type of operation to Caesarean section morbidity and septic mortality. Examination of the literature shows much discussion concerning the merits of the various operations. At the Philadelphia Lying in Hospital 409 sections have been performed during the last 3 years, with 3 deaths. There was no routine type of operation and the types performed were: classical section, 286 cases, Kerr cervical section, 103 cases, Porro's operation, 15 cases, Water's operation, 5 cases. The author relates that septic infection was the cause of one-third of the number of all the postoperative Caesarean section deaths. He made the assumption that it is unusual for a patient to die from sepsis unless the postoperative course has been morbid, and he studied the relation of the type of operation to postoperative morbidity. Classifying the cases according to the duration of labour Briscoe found that the lowest morbidity rates occurred in both low and classical sections if operation was carried out prior to the onset of labour. Low section has a lower

morbidity rate during labour except in the group 0-12 hours of labour, and he notes that classical sections were usually performed early in that period and low sections late. There was a 100 per cent morbidity rate in 6 cases of classical section after labour had progressed for longer than 12 hours. When the membranes had ruptured the morbidity was lowest in the low section operation. There was no appreciable difference in operative time between the two operations. In 15 Porro operations, all clean cases, the morbidity rate was 13.3 per cent. Analysing 114 septic deaths after Caesarean section during the years 1931 to 1942, in Philadelphia, Briscoe found that the absolute and relative death rates were in favour of low section. The death rates from Porro operations in the city compared unfavourably with reported series of extraperitoneal operations, and he considers that in an infected patient an extra-peritoneal section offers the best chance.

Episiotomy

Indications

Flew discusses the value of episiotomy in diminishing trauma of the vaginal passage during the second stage of labour. A perineal tear involving the rectum must be avoided at all costs. To have no perineal tear does not rule out internal unseen damage. Overstretching and tearing of the deep-seated fibres lessen their ability to regain their tone and lead to prolapse of the vaginal wall even with an intact perineum. The operation should be carried out when the head bulges the perineum and should not be left until the perineum is only of tissue-paper thickness since by then the damage will have been done. The main indications for episiotomy are the occurrence of strong pains and lack of progress. The incision should start strictly in the midline and should reach to a point 1 inch from the anal margin. It is then continued in a curved direction towards the ischial tuberosity. Thus the sphincter is avoided and there should be no rectal tear. The incision should be made at the height of a pain and may be done without anaesthesia. Results in 135 consecutive primigravid private patients show that episiotomy was performed in 53.3 per cent. Forceps deliveries were 12.6 per cent, all with episiotomy. Of the 72 episiotomy cases, 2.8 per cent had subsequent symptoms of vaginal prolapse and in the 63 normal cases without episiotomy these symptoms developed in 8 per cent.

Briscoe, C. C. (1944) *Amer. J. Obstet. Gynec.*, 48, 16.

Flew, J. D. S. (1944) *Brit. med. J.*, 2, 620.

Mackie, Margaret A. (1944) *Med. J. Aust.*, 2, 428.

LABOUR: ANAESTHESIA AND ANALGESIA

See also B.E.M.P., Vol. VII, p. 573; and Cumulative Supplement, Key Nos. 895 and 896.

Anaesthesia and analgesia

Methods of administration

Continuous caudal anaesthesia.—In a commentary, Baptisti discusses continuous caudal anaesthesia. He relates that in 1938, after a critical study of the subject at the Baltimore City Hospitals, it was confirmed that continuous analgesia and anaesthesia could be obtained by single injections of anaesthetic introduced at appropriate intervals of time into the caudal canal. After a study of a small series of cases in which this method of anaesthesia was used, starting at different stages of labour, it was found that when the presenting part was deeply engaged cervical dilatation progressed satisfactorily, but when it was not, the first stage of labour was sometimes retarded and the second stage was often retarded and sometimes arrested. Some descent took place but arrest occurred in the low pelvis, and then two courses were open: delivery by forceps or normal completion of labour after the patient had been allowed to come round. The type of forceps delivery necessary was higher than that which can be termed an outlet forceps delivery. The conclusion was drawn from this series that caudal anaesthesia interfered with the normal mechanism of labour and was not advisable for the relief of pain in the first and second stage of labour. It was concluded, however, that in certain selected cases of operative delivery caudal anaesthesia has many desirable advantages; in these cases a single injection is usually sufficient. Its use as a routine delivery anaesthetic was not justified. The author relates that in the six hundredth case of a series subsequent to this study, in which caudal anaesthesia had been used as a routine delivery anaesthetic, administration resulted in an accidental intradural injection with sudden respiratory failure; the patient was resuscitated after 20 anxious minutes. In two other large maternity clinics in Baltimore, each of which tried caudal anaesthesia in a series of cases, one death occurred in each series and as a consequence the use of caudal anaesthesia was abandoned. Further investigations showed that the incidence of comparatively high pelvic arrest mentioned above was a sampling error, but it seems to be clear that the incidence of operative obstetrics is increased. Baptisti stresses that the ideal anaesthetic in obstetrics is one which does not cause an increase of operative deliveries. The risks of caudal anaesthesia are no less today than they were previously. The indwelling catheter and needle have not made the dangers less but have increased the risk of infection, of breakage of the needle and of dural penetration. The possibility of late effects on the nervous system remains unknown. Another practical disadvantage of the general use of caudal anaesthetic is the time taken up by the procedure. Baptisti considers that the elective use of a procedure so hazardous for the purpose of relieving the pains of labour is not justified.

LACRIMAL APPARATUS DISEASES

See also B.E.M.P., Vol. VII, p. 592.

Diseases of the lacrimal gland

Mikulicz's disease

Report of a case.—Miller, Eusterman and Leddy report on an example of Mikulicz's syndrome with associated gastric and pulmonary lesions in a 74-year-old man who complained of (1) protrusion and irritation of the eyes; (2) dyspnoea and generalized weakness which had been progressive for 9 months; (3) increased lacrimation, photophobia and reddening of eyes, all of which were worse in the morning; (4) bilateral symmetrical exophthalmos; (5) general fatigue, but without symptoms typical of exophthalmic goitre. The basal metabolic rate was found to be +22. Lugol's solution of iodine was administered; exophthalmos progressed and soft nodular swellings appeared insidiously on the eyelids, in the left temporal region and over the left mastoid process; there was fullness in the left submaxillary region. The patient gave a history of recurrent dyspepsia for 40 years and recurrent non-specific conjunctivitis for 10 years. Skiagraphs of stomach and lungs suggested the presence of carcinoma. Biopsy of an orbital nodule led to a diagnosis of Mikulicz's disease; the diagnosis was revised later to that of lymphosarcoma of low grade malignancy. Orbital and pulmonary lesions responded so favourably to x-ray therapy (the lung condition resolved almost completely) that it was decided to treat similarly the gastric lesion; this also disappeared almost completely. The liver, but not the spleen, remained palpable. Leddy regarded and treated the syndrome, from the radiological point of view, as that of lymphoblastoma, but he gave light doses and included the orbits and the salivary glands.

Lacrimal obstruction

Acquired

Transplantation of the sac.—Gifford, basing his discussion of dacryocystitis on 88 cases in adults and 37 in infants, states that the first sign is epiphora, which may be followed by conjunctivitis and corneal ulceration. In infants failure of the nasolacrimal duct to open after birth results in infection and the development of a mucocele. Out of 37 cases Gifford states that 19 patients recovered after daily pressure had been exerted on the sac in order to empty it, and the application of a mild antiseptic. Of the other 18, all except 4 recovered after probing of the duct; the 4 failures appeared to be due to too early interference. Probing should not be done before the age of 6 months. Gifford gives a list of the most common causes of dacryocystitis in 125 adults, and states that although the aetiology is not as simple as is that in the infant, he believes the primary cause to be obstruction to the flow of the tears. If conservative treatment fails the sac must be incised. If the sac atrophies no further treatment is necessary unless there is excessive lacrimation, but a mucocele or fistula will need dacryocystorhinostomy. The sac should be removed only in cases of tuberculosis, tumour or leukaemia. Otherwise Gifford advises transplantation of the sac by means of a technique which frees the lower end externally, trephines an opening into the nose and holds the open lower end of the sac in place in the nose by sutures pulled out on the cheek. In his series Gifford records 68 successes out of 88 cases; the reason for failure was either faulty technique or anatomical abnormality.

Gifford, H., Jun. (1944) *Arch. Ophthal.*, N.Y., 32, 485.

Miller, J. R., Eusterman, G. B., and Leddy, E. T. (1944) *Proc. Mayo Clin.*, 19, 425.

LARYNX DISEASES

See also B.E.M.P., Vol. VII, p. 612; and Cumulative Supplement, Key Nos. 918-927.

Acute laryngitis

Laryngo-tracheobronchitis

Treatment of acute conditions.—Baum discusses the treatment of acute laryngo-tracheobronchitis. He believes that the complaint is probably due to a virus with secondary invasion by other pathogens, notably streptococci. Sulphonamide therapy in his experience has been unsatisfactory. Penicillin therapy may be more successful, but has not yet had a sufficient clinical trial. Baum considers that injections of human immune influenza serum, preferably from a contiguous case, give the best results, steady improvement usually starting 24 hours after injection. Apart from the general treatment of the infection local emergency treatment may be needed for the purpose of relieving respiratory obstruction due to subglottic laryngeal oedema. Baum advises that tracheotomy should not be immediately performed in these cases but that it should be preceded by laryngoscopy without anaesthesia, when it may be possible to relieve the obstruction by aspiration of false membranes or mucous plugs which may fill the whole tracheobronchial tree. Bronchoscopy might be necessary for more extensive treatment and great care must be exercised during its use in order to prevent trauma. Oxygen can be administered through the bronchoscope, if necessary. Intravenous injection of 25-40 cubic centimetres of 4 times concentrated hypertonic human plasma combined when practicable, in the treatment of adults, with preliminary venesection may help to reduce subglottic oedema. If such measures do not give immediate relief, intubation or tracheotomy must be performed. Intubation, since it avoids the drying effect of air inhaled through a tracheal cannula, is to be preferred although it requires the constant presence of skilled medical aid. Such dry air dries the bronchial secretions and thus forms adhesive obstructive plugs which

LEPROSY

See also B.E.M.P., Vol. VII, p. 682; and Cumulative Supplement, Key No. 935.

Prognosis

Erythrocyte sedimentation test

Evaluation as a prognostic measure.—Faget, describing a statistical study of more than 2,000 tests performed on more than 500 patients, discusses the evaluation and significance of the erythrocyte sedimentation test in leprosy. Investigators disagree about its significance. Some relate it to the type of leprosy, reporting it as being rapid in the nodular and mixed types and as nearly normal in the neural form. Others use it as a measure of the patient's tolerance of medication, especially of the iodides. Faget himself has found the erythrocyte sedimentation rate to be raised in all cases of leprosy, to the greatest extent in lepromatous and mixed cases but, with rare exceptions, to some degree also in neural and tuberculoid types. Even in long arrested cases it is seldom normal. At the National Leprosarium in the United States of America the erythrocyte sedimentation rates are divided into zones of varying prognostic significance as follows: (1) 0–10 millimetres, the normal, or arrest, zone; (2) 11–20 millimetres, the zone of quiescence or slight activity; (3) 21–25 millimetres, the zone of moderate activity; (4) 26–30 millimetres, the zone of severe activity; (5) 31–40 millimetres, the danger or death zone of advanced leprosy. Single tests are of little value but curves, based on serial tests over a number of years, have proved to be significant as indicating the course of the disease. (1) A horizontal sedimentation curve indicates a prognosis dependent upon the height of the curve, (2) an irregular curve indicates a guarded prognosis, (3) an ascending curve indicates a poor prognosis and (4) a descending curve indicates a good prognosis. At the National Leprosarium, however, variations in the sedimentation rate have been found to be of little value as an indication of reaction to treatment. In leprosy there is hyperglobulinaemia; the author considers that the tissue destruction which occurs causes both this and the raised erythrocyte sedimentation rate.

Treatment

Curative

Use of grenz rays.—Sagher discusses the treatment with grenz rays of two cases of leprosy. The rays have only slight penetrating power, unlike roentgen and radium rays which are known to cause great damage to the surrounding skin and deep tissues. In two cases of a mixed type of leprosy causing extensive infiltration of the skin, the patients were given doses totalling between 600 and 7,000 roentgens at a maximum voltage of 6–14 kilovolts. The skin lesions were divided into small areas, an area of clinically normal skin being included, and each area was given doses varying from fractional to larger applications spread over different periods of time. Doses under 2,000 r were found to be ineffective, but over that amount the infiltrating lesions gradually disappeared until after from 4–12 months no clinical symptoms remained. The author also found that with the exception of the normal skin, the areas treated by this method were proof against invasions by new lesions. After $1\frac{1}{2}$ – $2\frac{3}{4}$ years, no damage other than occasional patches of pigmentation was found, with the exception of one area which had received a single dose of 5,000 r and showed severe atrophy with telangiectasis. Sagher concludes therefore that massive doses should be avoided. Grenz rays do not inhibit the growth of the causative organisms since *Bacillus Hansenii* was found in all treated lesions. He believes that grenz rays may be of value in localizing skin lesions, particularly those of the face which would otherwise cause the patient great distress.

Review of treatment.—Cochrane, describing the treatment of leprosy, gives a preliminary account of its pathology. The *Mycobacterium leprae* attacks tissues developed from primitive ectoderm and if all resistance fails, as in lepromatous leprosy, the bacilli can spread through the reticulo-endothelial system to attack any part except vital organs. Treatment should aim at assisting the natural defences. In tuberculoid leprosy, foci or tubercles similar to those of tuberculosis are seen, and it is believed that they indicate a process by which they are anchored in the skin and are thus prevented from spreading further. Tuberculous leprosy can be treated by weekly or semi-weekly intradermal injections of a preparation of hydnocarpus oil into the lesion, no lesion receiving more than one injection monthly. Each cubic centimetre of skin requires 6–12 injections. In simple macular lesions of neural leprosy in which hypopigmentation is present, the areas can be painted with 1·3 trichloroacetic acid or intradermal injections of hydnocarpus oil to establish pigment can be given. In lepromatous leprosy the bacilli should be rendered inactive as soon as possible and Cochrane considers that repeated courses of intradermal and subcutaneous injections of hydnocarpus oil are most efficacious; he also emphasizes the need for perseverance in treatment. Potassium iodide should never be given. Nodules in advanced cases can be reduced with solid carbon dioxide and lepromatous ulcerations can be treated by small courses of gold injections. In advanced lepromatous leprosy subcutaneous nodules should be removed before they have a chance to ulcerate. Pendulous and enlarged ear lobes should be trimmed under local anaesthesia and the raw edges painted with pure phenol. Cochrane describes the lepra reaction and goes on to discuss in detail the treatment of iritis in leprosy. In an acute attack, the patient should be put to bed and purged with calomel and saline; the pupil should be rapidly dilated with atropine. Sedatives and hot compresses should be given for the pain, and the application of a leech is often most effective. Intramuscular injections of milk protein may help. All operative procedures involving an incision into the cornea should be avoided unless total

loss of vision is threatened since the results do not otherwise warrant the taking of the risks involved. Cochrane concludes by advising that trophic ulcers should be kept clean and, if there is not bone involvement, that they should be injected with hydnocarpus oil. If amputation of lower limbs becomes necessary a weight-bearing stump should be preserved because deformity of the hands often precludes the use of crutches. Deformities from muscle wasting can be improved by movement, and by the use of faradism and diathermy.

Cochrane, R. G. (1945) *Med. Pr.*, 213, 295.

Faget, G. H. (1945) *Ann. intern. Med.*, 22, 213.

Sagher, F. (1944) *Arch. Derm. Syph., N.Y.*, 50, 311.

LEUKAEMIA

See also B E M P, Vol. VIII, p. 1, and Cumulative Supplement, Key Nos. 940-955.

Lymphocytic leukaemia

Chronic lymphocytic leukaemia

Scott and Lissimore describe treatment of mesenteric thrombosis in lymphatic leukaemia with Dicoumarol (dicoumarin). An active builder aged 62 years had been apparently healthy until at the age of 45 he became short of breath when climbing ladders and felt fatigued by the end of the day. From July 1941 until the 26th of February 1942 he had intermittent attacks of cramp like abdominal pain and vomiting and sometimes diarrhoea. At laparotomy on the latter date, for a condition which was diagnosed as "an acute abdomen", a thrombosis in a branch of the superior mesenteric artery was found to be causing acute obstruction of the terminal ileum. The spleen was enlarged. Postoperative shock and collapse led to blood grouping for transfusion and Lissimore made a full blood count which revealed lymphatic leukaemia. X-ray treatment greatly improved the blood picture but attacks of mesenteric thrombosis persisted and later there were signs of an intracranial thrombosis. The administration of heparin was impracticable and it was decided to give Dicoumarol. One capsule containing 0.05 grammes given on alternate days from 25th June to 27th November 1943 lowered the prothrombin index from 92 to 60. The patient has had occasional mild attacks of abdominal pain since the commencement of the Dicoumarol treatment.

Scott, R. A. M., and Lissimore, N. (1944) *Lancet*, 2, 405.

LIVER DISEASES: LIVER FUNCTION TESTS

See also B E M P, Vol. VIII, p. 81, and Cumulative Supplement, Key No. 967.

Tests

Nicotinamide test

Methylation of nicotinamide—Najjar, Hall and Deal advocate the use of a liver function test based on the methylation of nicotinamide. In experiments on dogs the liver was infused with a nicotinamide solution. There was an immediate increase in N^1 methylnicotinamide in the liver tissue and in the blood draining therefrom. The capacity of the liver to methylate the vitamin appeared to be remarkably high. In contrast, the kidney was found to play no part in the process. Large doses of nicotinamide were given by the mouth to normal human subjects. The results suggested that in man the methylation process in the liver is apt to manifest signs of impairment and exhaustion. Other experiments were performed on patients by means of a load test of either 50 milligrams of nicotinamide by the mouth or 20 milligrams of the vitamin injected intravenously. The ability to methylate was studied by measuring the urinary output of methylated nicotinamide. In every case test doses of nicotinamide produced a higher degree of methylation by intravenous injection than by oral administration. However, both methods showed that patients with no liver involvement possessed a greater capacity to methylate than those suffering from hepatic disorders. The most striking results were obtained in 3 cases of glycogen disease. All 3 patients showed a very low output of N^1 methylnicotinamide. Similar effects were noted in 2 patients with catarrhal jaundice who were studied during convalescence, and in one of 3 cases of nephrosis. The values were somewhat low in 4 out of 5 patients with diabetes mellitus.

Najjar, V. A., Hall, Rowena S., and Deal, Carolyn C. (1945) *Johns Hopk. Hosp. Bull.*, 76, 83.

LIVER DISEASES: BLOOD-VESSELS

See also B E M P, Vol. VIII, p. 87.

Hepatic veins (obstruction and occlusion)

Clinical picture

Some light on the cause of Chiari's disease—Armstrong and Carnes report on 5 cases of obstruction of the hepatic veins (Chiari's disease). The first case was that of a 28 year old male with habitual bronchopneumonia, right sided abdominal pain and marked liver enlargement. The Wassermann reaction was negative and the erythrocyte count 4.8 millions. Post mortem examination showed a liver abscess and recent thrombi in several large hepatic veins. In two cases the thrombosis was associated with malignant disease—in one there was a metastatic gastric carcinoma and in the other a hypernephroma had disseminated along the whole inferior vena cava and involved all the branches of the hepatic vein. A fourth case was that of a 55 year-old man with a history of alcoholism. He had had ascites and repeated haematemeses, the Wassermann reaction was positive. Postmortem examination showed a

small liver, collateral veins to left kidney, abdominal wall and diaphragm, and varicose oesophageal veins, several being perforated. The portal vein was filled with organizing thrombus and both right and left hepatic veins were thrombosed. The fifth case occurred in a 40-year-old woman who gave a positive Wassermann reaction and no history of alcoholism. The liver was enlarged, the blood pressure was raised, there was ascites and icterus and a mild polycythaemia; the bone marrow was hyperplastic. *Post mortem*, the liver was enlarged and there were numerous small scattered areas of haematopoiesis. The main hepatic veins showed organizing thrombi, with some degree of recanalization at their margins. Obstruction of the hepatic veins should be considered in any patient who has progressive tender enlargement of liver and spleen with ascites and abdominal pain.

Armstrong, C. D., and Carnes, W. H. (1944) *Amer. J. med. Sci.*, 208, 470.

LIVER DISEASES: HEPATITIS, ACUTE AND SUBACUTE

See also B.E.M.P., Vol. VIII, p. 104; and Cumulative Supplement, Key. No. 973.

Clinical and aetiological types

Infective hepatitis

Clinical types.—Damodaran and Hartfall review 450 cases of infective hepatitis treated in Malta from 1941 to 1943. The disease, which was indistinguishable from catarrhal jaundice, became epidemic in the autumn and was probably due to a virus. Overcrowding and droplet infection were important aetiological factors. The majority of cases occurred in the third decade and in the fourth week after exposure to infection. Four clinical types were recognized but, in 52 per cent of the patients, jaundice was accompanied by gastro-intestinal symptoms. The remaining groups consisted of the febrile and ambulatory types, and the type without jaundice. There was one fatal case of icterus gravis but the less serious condition of subacute hepatic necrosis was more often encountered. Derangement of liver function was indicated by the low prothrombin content of the blood. Second attacks of jaundice were noted in 2 patients, and relapses were precipitated by too early discharge from hospital or by bouts of alcoholism. It was apparent that alcohol hastened the onset of jaundice in persons incubating the disease, a fact of importance in the consideration of prophylaxis. Fourteen instances of jaundice occurred in syphilitic patients treated with arsphenamine and, in this respect, the effect of arsenic was more pronounced than was that of alcohol. Similarly, injections of gold compounds have accentuated the severity of infective hepatitis. It was deduced from the clinical findings and necropsies that the jaundice is partly obstructive in nature. The obstruction lies in the hepatic parenchyma and not in the biliary canals.

Clinical course.—Havens reviews 200 cases of infective hepatitis in a hospital in the Middle East and emphasizes its military importance owing to the average 28-day period of stay in hospital. The author describes the clinical course of the condition under respectively pre-icteric and icteric stages, and stresses the diagnostic difficulties often encountered during the former and the need for urine examination; he states that "the importance of biliuria cannot be overemphasized, and daily gross examination of the urine by the medical officer himself for bile did much to establish early diagnosis before clinical jaundice was evident". The commonest and normally the first symptom was anorexia, followed later by nausea, and sometimes by vomiting which occurred just before the appearance of jaundice. One hundred and sixty-seven patients manifested a pre-icteric phase and in approximately half the number of these onset was sudden with chills, fever, malaise, headache and general aching. Temperature was usually remittent, with a peak at 102° F. Daily chills, with temperature of 103–104° F., aching eyes and pain on movement of eyeballs caused confusion with sandfly fever, and repeated chills with high fever, nausea and vomiting suggested malaria. Clinical jaundice appeared between 24 and 48 hours after temperature became normal. In 38 patients jaundice was the first complaint without any preceding symptoms or signs. The constant anorexia came to be regarded as a very reliable diagnostic symptom of infective hepatitis. Liver tenderness and enlargement usually synchronized with the appearance of jaundice. Treatment was symptomatic. Duodenal drainage had apparently no beneficial effect. Sodium sulphate, 4–1 ounce taken in warm water before breakfast, relieved both constipation and the sense of fullness and epigastric oppression of which some patients complained. The only complication observed was seborrhoeic dermatitis. In 6 men treated with arsenicals or bismuth within 3 months before onset of jaundice, the period of jaundice was prolonged beyond the average length of time.

Problems still to be solved.—Altschule and Gilligan present findings in a series of 36 unselected persons who had had infective hepatitis between one and 29 years before their cases were studied. Plasma bilirubin levels ranged between 0.23 and 3.01 milligrams per 100 cubic centimetres, 16 patients having values above 0.62 milligram, and 9 having values above 0.82 milligram. The plasma bilirubin concentrations of 36 control subjects ranged from 0.08 to 0.82 milligram per 100 cubic centimetres, only 4 persons having values above 0.62 milligram. Clinical findings included icteric scleras in 7 patients, 1 palpable spleen and 9 palpable livers. Discussing the sequelae of infective hepatitis, excluding those manifesting immediately or shortly after an attack, the authors consider that hyperbilirubinaemia persisting for years—as it was found to have done in 25 per cent of their cases—indicates an incidence of chronic mild impairment of liver function even greater, since the distribution of plasma bilirubin

transmission of infective hepatitis by the oral route. It appears that the infective agent, probably a virus, is present in the blood stream before the onset of jaundice and during it, and in the acute stage in the faeces as well as probably in nasal washings. The agent is transmissible to man and is probably identical with that of serum jaundice; it is filtrable and markedly heat stable. Experiments now suggest that serum jaundice can be transmitted by nasopharyngeal washings, and important discoveries indicate that in infective hepatitis—of which the incubation period is about 30 days—the virus is in the faeces. This material when fed to volunteers or sprayed into the nasopharynx induces the disease after 27–31 days. The feeding of 3 volunteers on icterogenic serum in gelatin capsules caused hepatitis in 2 of them within 30 days and in the third after 84 days. Pooled icterogenic serum when inoculated intracutaneously into 5 volunteers caused hepatitis in 3 of them after 56–70 days but, when given by the mouth, failed to induce the disease in 3 volunteers. Infective hepatitis can be transmitted by feeding volunteers either with faecal material or with the serum of infective hepatitis patients.

Arsphenamine jaundice

Dangers of the unsterilized syringe.—Sheehan reports observations made on several groups of patients on the possibility of transference of jaundice by unsterilized syringes during intravenous therapy. In group (1) there was a 50 per cent incidence of jaundice among 200 men who were receiving neoarsphenamine intravenously from syringes washed but not sterilized between injections. In group (2) only 2 out of 80 women contracted jaundice in a syphilis clinic in which syringes were sterilized by 15 minutes' immersion in strong antiseptic and these 2 had received additional treatment elsewhere. Group (3) consisted of patients at a syphilis treatment centre at which in three-quarters of the number of men jaundice developed; in 5 who were treated with carefully sterilized syringes and meticulous precautions the condition did not develop although they were observed for from 15 to 27 weeks. Group (4) included 2 batches of men who were receiving treatment for syphilis, on Wednesdays in the case of one batch and on Fridays in the other. A man who was in the incubation stage of hepatitis was admitted to the Wednesday group and in the subsequent weeks in 8 other men jaundice developed. No member of the Friday section was affected. In group (5) were orderlies and laboratory technicians who handled blood from treatment centres. In 6 of these men, none of whom had had injections, jaundice occurred. Group (6) consisted of 85 patients from a tuberculosis sanatorium in whom jaundice had developed over a period of 5 years. The author's study of these groups leads to the determination of a minimum incubation period of 10–12 weeks. He believes blood to be highly infectious within 3–4 weeks from the commencement of incubation. These findings accord with what is known of hepatitis transmitted by vaccines and sera.

Other forms of acute and subacute hepatitis

Jaundice supervening on vaccination for yellow fever.—Hayman and Read describe an outbreak of jaundice which occurred after yellow fever vaccination. The disorder affected 398 men, and there were 2 deaths in the series. The mean interval between vaccination and jaundice was 100.1 days. Jaundice was the presenting complaint in 273 cases, but the onset was often insidious, with anorexia, epigastric discomfort and dark urine. The incidence of upper respiratory symptoms at the onset was considerably less than is usually encountered in epidemics of infective hepatitis. Unusual drowsiness occurred in 21 patients and, in some cases, sleep was almost continuous for several days. Urticaria was an early manifestation in 10 instances, but even the deeply jaundiced patient rarely complained of itching. Other skin disorders included erythema, maculopapular eruptions, purpura and spider telangiectases. Pyrexia was recorded in only 17 per cent of the cases, and bradycardia was uncommon. There was moderate enlargement of the liver, and the spleen was palpable in 26 patients. The onset of convalescence was sometimes heralded by a profuse diuresis. Albuminuria occurred in 18.5 per cent of the cases, but bile salts were never detected in the urine. The stools were rarely alcoholic, although an abnormally light colour was common at the height of the disease. The mean of the maximum icteric indices was 64.4. In a small group icteric indices were determined at approximately weekly intervals. It was found that, after the beginning of convalescence, the chromogenic material in the serum diminished at a more rapid rate during the first few weeks than it did in the later stages. The blood counts and sedimentation rates were normal. From clinical observations it was considered that the cephalin-cholesterol flocculation test was of value in determining the degree of active liver damage. This test became negative before urobilinogen disappeared from the urine. Bile was present in the duodenum in cases intubated at all stages of the disease. Examination of the duodenal contents gave no clue to the nature of the aetiological agent. High carbohydrate diets were of doubtful value in the milder cases, but good results were obtained by giving glucose to patients with severe disease.

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Damodaran, K., and Hartfall, S. J. (1944) *Brit. med. J.*, **2**, 587.

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 Sheehan, H. L. (1944) *Lancet*, 2, 8
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LIVER DISEASES: HEPATITIS, CHRONIC

See also B E M P, Vol VIII, p 118, and Cumulative Supplement, Key No 974

Morbid anatomy and pathogeny

Liver

Experiments on rats to show relationship of ceroid to various oils—Endicott, Daft and Sebrell report on experiments on rats in which cirrhosis of the liver developed without the production of the insoluble pigment, ceroid. The rats were given purified diets containing palmitic, stearic, oleic, linoleic and linolenic acids. Each animal received a supplement of vitamins. The cirrhotic livers showed fibrous trabeculation, distortion of lobular architecture, and deposits of large globules of fat in the hepatic cells. The results indicate that the important dietary precursor of ceroid is not an ingredient of Wesson (cottonseed) oil but is contained in cod liver oil. Ceroid resembles the lipid residues in pneumonia due to cod liver oil. Similar substances can be produced by chromate oxidation of cod liver oil and linseed oil but not by oxidation of various hydrogenated oils. Apparently, the type of fat in a diet poor in choline and protein has an important influence on the deposition of the pigment. Ceroid has not been reported as having been found in the human liver and experiments have failed to demonstrate the substance in the dog, guinea-pig, pig or rabbit. It is of interest to note that hepatic cirrhosis may be produced in rats on diets completely devoid of fat or fatty acids.

Clinical picture and clinical types

Chronic hepatitis with predominant portal obstruction (common portal cirrhosis)

Review of symptoms and treatment—Chaikin and Schwimmer discuss the clinical and therapeutic evaluation of portal cirrhosis, which they define as 'a progressive destructive process characterized by atrophy, fatty degeneration and necrosis of individual liver cells, with proliferation of new connective tissue and regeneration of new lobules'. The problem of aetiology is complicated by the untruthfulness of alcoholics. Of the 246 cases investigated 104 gave an alcoholic history, approximating to the 54 per cent in Ratnoff and Patek's cases. Malnutrition is an important factor. Early diagnosis is difficult—owing to vagueness of early signs and symptoms—but highly important in order that early treatment may be instituted. Bleeding may be the sole early expression of the cirrhotic process. Five cases were admitted to hospital primarily for epistaxis. In the absence of jaundice, hepatosplenomegaly or history of alcoholism or malnutrition, laboratory liver function tests may be of great value in establishing or corroborating diagnosis and in prognosis. In 108 of the cases the patients were jaundiced and the direct van den Bergh reaction was delayed in 69 per cent, biphasic in 22 per cent and immediate in 9 per cent. The test aids prognosis but not diagnosis. The cephalin-cholesterol flocculation test indicates active hepatic pathology. Less than 65 per cent of cholesterol esters is considered to be abnormal and 55 per cent of non-jaundiced patients and 86 per cent of jaundiced patients displayed such results. In modern treatment liver function is aided by a diet containing large amounts of carbohydrate, protein and vitamin B complex and a small amount of fat. Of 32 patients 8 lost the ascites and appeared to be in good health as compared with 2 out of 44 patients on the old regimen. Early cases results

Treatment

Choline

Effect of choline chloride given after meals—Russakoff and Blumberg consider that there is justification for the use of choline as an adjuvant to the dietary in cases of cirrhosis of the liver. It appears that the patients most likely to respond favourably are those with the fatty type of hepatic cirrhosis produced by alcoholism. Ten patients were given a high calorie diet rich in proteins, carbohydrates and vitamins but poor in fat. To this diet was added choline chloride dissolved in peppermint water and administered daily in divided doses after meals. In the later stages of treatment the dosage was increased to 6 grammes of choline per diem. No unfavourable reactions were observed except in one patient in whom nausea developed after 0.5 gramme of the preparation had been taken without food. A very slight fall of blood pressure was noted and there was a slight decrease in the pulse rate. No untoward effects occurred in another patient who took the maximum dosage daily for 6 months. Improvement was gauged by changes in the clinical manifestations such as the reduction of the amount of ascites and a diminution in the size of the liver. Other favourable criteria included various tests showing an increase of the serum albumin and improvement in the liver function. Seven patients improved, but the speed of response was variable. In some cases beneficial effects were observed as early as the first week after the commencement of treatment. Three patients taking the diet did not begin to improve until choline was added.

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LUNG DISEASES: TUBERCULOSIS

See also B.E.M.P., Vol. VIII, p. 182; and Cumulative Supplement, Key No. 988.

Clinical Picture

Signs

Methods of investigation of a sanatorium staff.—Edwards, Penman and Blair describe methods of investigation and supervision applied individually to members of the staff of the Cheshire Joint Sanatorium. Routine examination of new staff includes clinical examination, tuberculin testing, radiological examination, weighing and estimation of blood sedimentation rate. The graduated intradermal Mantoux test, with purified protein derivative, is performed monthly in negative cases and results suggest that, although it is an unsatisfactory individual test, a large-scale survey might prove to be significant. New entrants are examined radiographically on joining the staff, then monthly until the Mantoux test becomes positive, and thereafter half-yearly although the authors consider that, without clinical evidence of activity, regression of the primary lesion is of purely academic interest. Blood sedimentation readings, which are always taken at the second hour, are carried out monthly until at least 3 months after the Mantoux test becomes positive and thereafter synchronously with each radiological investigation. In uneventful cases the blood sedimentation rate increases when the tuberculin reaction becomes positive but returns to the patient's normal level a month later. In non-retrogressing or complicated cases the rate remains rapid or returns slowly to normal. Weighing has not proved helpful in investigating primary tuberculosis. Thirty per cent of non-tuberculous entrants to the resident staff of the hospital were tuberculin negative. In no tuberculin positive entrant did tuberculosis develop. Recovery of 9 patients from primary infection was delayed or was accompanied by clinical illness in which symptoms or signs other than those of increased blood sedimentation rate or an uncomplicated retrogressing primary complex, were manifested.

Prephthical lesions.—With the object of impressing its importance upon the general practitioner, Mayer and Rappaport emphasize the problem of "prephthical" lesions which they define as "tuberculous lesions in the chest which precede the development of chronic pulmonary tuberculosis". The authors' criteria for the diagnosis of the condition are (1) recently acquired tuberculin sensitiveness with or without radiological evidence of lung infection; (2) recently resolved simple pleurisy with effusion, which has left no localized lesion in the lung after resolution; (3) radiological evidence of a persistent but stable round focus or smudge focus in the lungs. The authors plead for a new and less confused system of classification of types of prephthical lesions and claim that the terms, primary or first infection type, and reinfection type, have in the light of recent knowledge quite lost their meaning. In any event, differentiation between the prephthical lesions and chronic pulmonary tuberculosis may be difficult because the latter, when in process of healing, but still capable of exacerbation, may be indistinguishable from the former. Treatment presents an even greater problem because the vast majority of tuberculous lesions remain prephthical and become resolved or remain obsolete healed lesions, and there is no conclusive evidence that all such lesions are affected by treatment. Moreover, in the present state of knowledge there is a danger of overtreatment of the above-mentioned and of inadequate treatment of frankly tuberculous lesions. Whether strict rest in bed is or is not physically harmful to the prephthical patient, it is often psychologically bad. Prolonged observation and frequent radiological investigations are essential in these cases.

Pleural effusion and tuberculosis.—Robson discusses the relation between primary pleural effusion and tuberculosis. The French school, following Laennec, emphasized the close relationship between the two. Laennec recognized that there might be a period of good health after the pleural effusion and before the onset of clinical tuberculosis. Guineapig inoculations of pleural effusion produced tuberculosis. It was noted that some of these pleural effusion patients reached old age in good health. Many effusions are of a primary type yet continued observation of these cases reveals that in a proportion far in excess of the expected tuberculous morbidity of the general population tuberculosis develops at a later date. After the onset of a pleural effusion many weeks or months are spent in the process of stabilization, the patient, who is usually in early adult life, passing a vegetative existence in order to ensure himself against future tuberculosis. If no definite cause can be found many authorities believe that primary effusions should be considered to be tuberculous in origin. Arborelius, from examination of 20-year-old conscripts in Sweden, points out that the initial tuberculous infection may occur in early adult life, not in childhood. Environment plays an important part with regard to the age at which tuberculous infection shows itself. The highest incidence of primary pleural effusion occurs in early adult life. Evidence of even a small collection of pleural effusion should put the practitioner on his guard. The patient should be confined to bed for rest and endeavour should be made to stabilize his condition against possible development of the pulmonary foci. Any strain or stress may easily aggravate the condition. Convalescence should be established in pleasant surroundings with graduated exercises. The patient should

be kept under observation for 5 years with frequent clinical and x ray examinations. As regards aspiration of the fluid, the less done the better, but if aspiration is absolutely necessary, it should be carried out slowly.

Course and prognosis

Sedimentation test

Value in pulmonary tuberculosis—Davies discusses the sedimentation test and its historical and technical aspects, with particular reference to its value in pulmonary tuberculosis as a prognostic and therapeutic index. Using Westergren tubes, containing a column of blood 200 millimetres in length, the rate of fall of the erythrocytes is recorded after 2 hours, normal values being between 0 and 10 divisions, such a fall, in cases of proved pulmonary tuberculosis, indicates well established resistance and quiescent disease. A fall of between 10 and 20 divisions is given by patients whose resistance is in the balance, these are suitable for early sanatorium treatment. Patients showing a blood sedimentation rate fall of 20–40 divisions will usually require specialized therapy in either sanatorium or chest hospital before improvement occurs. Rapid advanced and complicated cases with well marked activity and slow response to treatment, give a fall of 40–60 divisions. The greater the fall beyond 60 the worse the outlook, in untreated cases. Sedimentation graphs, advantageously combined with weight graphs depict the clinical course and response to treatment, either symptomatic or by specialized therapy including thoracic surgery. Clinical improvement is followed by a decreased sedimentation rate, and a stationary course by a stationary graph, whereas exacerbations and complications are represented by an increased rate. Any form of therapy which does not improve the blood sedimentation rate should be abandoned as valueless. Patients should not be discharged from the sanatorium until their blood sedimentation rates have been established within normal limits, indicating arrested disease, since patients leaving the sanatorium with a rate of more than 10 divisions of fall are unlikely to do well. Increase of the rate occurs in the presence of pyrexia—irrespective of the causative factor—and pregnancy. Haemoptysis of pulmonary origin, indicative of activity, is associated with an increased rate unlike haemoptysis of extrapulmonary origin. An increased blood sedimentation rate excludes purely functional disease.

In young children

Primary disease and reinfection—Mitchell and Willis studied a group of 243 children admitted to a tuberculosis sanatorium. All had clear evidence of tuberculosis but in a considerable number of cases the distinction between primary disease and reinfection could not be made. Some cases of primary disease deteriorated and the patients died. In others, the primary disease cleared in the usual way and later there ensued an exacerbation which ran a course more allied to primary infection than to reinfection disease. The authors consider that there is great need of reassessment of these types, especially on account of the cases in which phenomena of reinfection or allergy occur a few weeks after the bacillus is introduced into the body. In both white and negro children the outlook was worse for the reinfection than for the primary type of tuberculosis, but in both types the negro child was found to have a much poorer chance of survival than had the white. Younger children, below 18 months, and Willis think it probable that almost any large community contains an appreciable number of children with pulmonary tuberculosis in which the lesions may be very extensive and the disease is classified as primary or as reinfection tuberculosis, these children are a serious threat to themselves or to their contacts. The evidence of this study suggests that hospital treatment is essential in such cases. Observation of patients subsequent to their discharge from hospital showed much less fatality in those who had been in hospital for longer than 3 months as compared with those who had been discharged earlier. Nearly all of the children admitted with active primary lesions who were kept in hospital until they could be discharged with the disease apparently arrested were found, over a long period of subsequent observation, to have remained well.

Diagnosis and differential diagnosis

X rays

Value of mass miniature radiography in detection of tuberculosis—Trail considers that mass miniature radiography provides the easiest method of instituting the first steps in the discovery of pulmonary tuberculosis in the supposedly healthy population. Examination of large numbers of persons proves that there is an alarming amount of unsuspected disease present at all ages, the incidence of inactive disease being roughly double that of active disease. Of those suspected because of abnormal films and later, on physical and bacteriological examination considered to have active disease, 35 per cent have not any symptoms. Correct investigation depends upon uniformity in the production of miniature films and accepted standards for full-sized films. Agreement must be reached on the clinical and radiological interpretation of early disease. At present the nomenclature is elaborate and the use of fewer terms would be advantageous. A central school is required for research into the normal and abnormal. The school would collect serial films of large numbers of individuals and would investigate such problems as the relation between childhood infection and the Auerbach focus. Consistent working throughout the country demands complete arrangements for ultimate diagnosis. The general practitioner would arrange for the tuberculosis suspect to

attend the dispensary and for the non-tuberculous patient to be examined at the nearest general hospital. Mass radiography would inevitably increase the work of the dispensaries and the tuberculosis officer would benefit by the provision of beds for observation of cases. It would be destructive criticism to suggest that the method involves unnecessary treatment or harmful worry, but there is a type of individual who will develop anxiety neurosis merely on being recalled for the taking of a large film. Preparations must be made for new forms of treatment. Thus discretion should be used in decisions which involve sanatorium residence for symptomless or sputum-free patients. Any new scheme should be comparable to the stage between sanatorium treatment and colonization as now practised at the Papworth Village Settlement, Cambridgeshire.

Acute pulmonary tuberculosis and mass radiography.—The various components of full chest investigation in order to establish a diagnosis of active pulmonary tuberculosis in individuals selected by mass radiography as requiring such investigation, are evaluated by Trenchard. A positive sputum is diagnostic. Evidence of toxæmia, pyrexia and increased blood sedimentation rate are often absent in early active tuberculosis; therefore these are not diagnostically valuable although they may be so prognostically. Often diagnosis depends upon a correlation of radiological and physical findings. Non-adventitious signs include the sternal-mastoid sign, diminished thoracic movement or percussion note; the presence of rales or sibili may indicate an active lesion. Repeated radiological examination may be necessary in order to differentiate between an Assmann focus and a localized pneumonic patch, an infarct or a secondary neoplasm, and between aberrant pneumonic areas and the proliferative type of tuberculosis. When cavitation has occurred, diagnosis of activity is usually possible from a positive sputum or from combined radiological and physical findings. If diagnosis is not possible, serial films should be taken at intervals of 6–12 weeks for at least 6 months, by which time, if there are neither radiological changes nor abnormal clinical findings, inactivity may be presumed. It is advisable to take precautionary films at intervals of 3 or 6 months over the succeeding 2 years. Active tuberculosis can exist without evidence of toxæmia and in the absence of complaints; some cases are likely to heal spontaneously. Their discovery by mass radiography, however, is highly desirable in order to permit of their observation and timely treatment, if required, and because they may be dangerous foci of infection for individuals who have poor natural resistance.

Report of an extensive investigation of chest lesions.—The various methods of conducting chest surveys for the detection of tuberculosis are discussed by Mason. He has personally reported on 5,000 paper films, over 2,000 4×5-inch films and over 300,000 35-millimetre films. When 35-millimetre films were used, at the Great Lakes training centre on the borders of the United States and Canada, the rate of radiography was maintained at an average of 240 cases an hour; the department included 14 x-ray technicians, 6 operating the machine and the others doing clerical work. If anything suspicious was found in the microfilm a check was made by taking a skiagram on a 14×17-inch film; if the diagnosis was then considered to be pathological the patient was sent to the Naval Hospital for assessment. In one 2-month period in which there was a total of 41,616 microfilms, 317 were rechecked; of these 112 were sent to hospital, and in 96 the diagnosis was confirmed. The reversal of the diagnosis in 16, according to the author was probably due to the fact that a pessimistic diagnosis was always made when there was doubt in order to minimize the errors which might arise when so small a film was used. Since the beginning of the survey out of a total of 400,263 examined by x-ray, 6 patients with active tuberculosis have been subsequently sent to hospital—2 after 2 months, 1 after 4 months and 3 after 6 months of service. Mason points out that there may be two explanations of these cases, (1) the small size of the film caused the lesion to be missed or (2) the condition developed subsequent to the taking of the film. The author states that the survey has been well worth while both for the patients and economically for the Government since out of 400,263 men 897 have been discharged from the service because of tuberculosis. He considers that a survey with a 4×5-inch film is best from the reliability viewpoint but that the 35-millimetre film is adequate for practical purposes.

Lipiodol bronchography

A substitute for tomography.—Dormer, Friedlander and Wiles discuss the investigation of those cases of pulmonary tuberculosis in which the sputum is positive but conventional anteroposterior skiagrams and lateral and oblique films do not disclose the actual site of the lesion or the source of the bacilli, and describe 5 cases in which the site of the lesion was demonstrated by lipiodol bronchography. Two cases showed dilatation of a bronchus, the third, a blocked bronchus feeding an area of pneumonitis, the fourth, bronchiectasis terminating in small cavities, and the fifth, an apical bronchus terminating in a cavity. The authors conclude that it is probable that bronchial block with subsequent pneumonitis and either abscess or bronchiectasis as a sequel is the common basic pathology in pulmonary tuberculosis. They also applied the same method of investigation to cases in which a part or the whole of a lung was obscured by previous inflammation of the pleura or after artificial pneumothorax or other forms of therapy and to those in which conventional radiographic methods failed to give a clear and detailed view of the lesions in the blacked-out area. Seven such cases were studied by bronchography and in all the lesions were revealed in detail. The majority of cases showed gross cavitation and Dormer and his associates think that block of a main bronchus with subsequent excavation of large portions of a lung is a not uncommon

sequel to pulmonary tuberculosis. In view of the size of the cavity and the great thickening of the pleura it appears that thoracoplasty would fail in such cases. This method of investigation by bronchography is claimed to be a reliable substitute for tomography, especially in small hospitals in which adequate apparatus is not available.

From carcinoma

Bronchiogenic carcinoma—Pillsbury and Wassersug, analysing the cases of 12 patients with bronchiogenic carcinoma who were admitted to a tuberculosis hospital, emphasize the diagnostic difficulties often presented by this condition. They also mention that 13 such patients, reported on by Moersch and Tinney, had spent several months in tuberculosis sanatoria before a correct diagnosis of their condition was made. The authors' 12 cases occurred in males aged between 40 and 68 years. Eighty per cent of Moersch and Tinney's patients were over 40 years of age. The disease occurs most often in the right lung and presents no characteristic syndrome. Pain, cough, expectoration and haemoptysis may all be present or absent. In all the cases described by the authors the patients had productive cough but neither the character of this nor the gross appearance of the sputum aided differentiation from various other pulmonary disorders. Five per cent of Moersch and Tinney's patients presented no symptoms referable to the thorax. Signs are exceedingly variable and never characteristic. Skiagrams usually simulate those shown by tuberculosis or may be negative in the presence of bronchiogenic carcinoma. Betts has described bronchoscopy as being "the most important method of diagnosis in primary carcinoma of the lung", owing to the rapid progress of the disease, however, it must be performed early. Carcinoma must be considered as a possibility in the diagnosis of pulmonary complaints in all males aged between 40 and 60 years.

Treatment

Prophylaxis

Programme of control campaign in America—Parran reviews the outlook for the conquest of tuberculosis in the United States of America. Much work has already been done, but the recent war, causing lowered resistance to the disease, made more strenuous and comprehensive measures necessary. Of a quarter of a million war workers and their families examined by the Public Health Service, 1.3 per cent have shown evidence of reinfection tuberculosis—62 per cent in the early stages, 31 per cent moderately advanced, and 7 per cent far advanced—and care is necessary in order to prevent further spread. Of nearly 60,000 persons dying of tuberculosis in the United States about half the number are in the most productive period of life, and about 130,000 young men and women were rejected for the armed forces because of tuberculosis. Alive to the necessity of coordinating the efforts of public and private agencies and utilizing joint resources under the stimulus of a national programme, the National Tuberculosis Association, the Public Health Service and the State health authorities have laid the foundations of such a programme. The essentials are: (1) x-ray chest examination including x-ray of chest, of persons with inactive disease, (2) periodic examinations for the entire population and follow up of every case discovered, (3) prompt treatment of early cases, (4) strict isolation of open cases in order to prevent spread of infection, (5) intensified health education of the general public patients and their families, (6) greater research in tuberculosis and method of control, (7) financial aid to the tuberculous breadwinner. Were such a programme to be carried out, Federal assistance to States would be given by the authorization of funds by Congress, State health authorities would lead in establishing tuberculosis control schemes and local health agencies would coordinate community resources, working with the local medical profession and welfare groups.

Experiments with Promin—Feldman and Hinshaw describe 2 experiments in the course of which tuberculosis was induced in guineapigs by human tubercle bacilli. Forty-two days after induction of the disease treatment was instituted with Promin and continued for 365 days in experiment (1) and 210 days in experiment (2). After an interval of 28 days about half the number of animals which had survived throughout the period of medication were reinfected with the same strain of bacilli and this reinfection phase of the investigation continued until all the animals had died. Untreated control animals were observed throughout the experiments which were made to determine whether Promin treatment enhances resistance after reinfection or exerts merely a temporary suppressive effect. The results of previous experiments had led to a tentative opinion that chemotherapy induced a degree of acquired immunity sufficient to suppress the activity of tubercle bacilli even when the chemotherapeutic influence had been withdrawn. In the present experiments each of 48 guineapigs was inoculated subcutaneously with 0.0005 milligram of a 17 day old culture of human tubercle bacilli strain H37RV. The Promin was added to the feeds in a strength of 1 per cent of the weight of the animals which amounted to an average daily intake of 400 milligrams. The treatment influenced favourably the course of the infection, mortality rate was lower amongst the treated animals than it was amongst the controls and the amount of disease in the treated animals which died averaged 16.8 as against 84.1 amongst the controls. Significant modification of the disease after reinfection did not occur and there was no evidence of development of drug fastness.

Importance of suitable occupation—The value of work in the treatment of tuberculosis is discussed by Heaf. Paterson at Frimley Sanatorium, Surrey, first introduced a system of rigidly and carefully graduated exercises, but patients became rapidly bored by the simple

and monotonous labour prescribed and consequently failed to cooperate in their treatment. Varrier-Jones at the Papworth Village Settlement, Cambridgeshire, encouraged the patient's will to work by the establishment of productive industries. Although psychologically this was an improvement, careful assessment of the patient's working capacity had later to be made in all cases lest his will to work became too great for his physical powers. The concurrent development of collapse therapy led in some cases to occupational therapy being completely ignored, whereas in others only unsupervised diversional therapy was carried on. The author believes that discipline is essential in the treatment of tuberculosis; the type of work should be on a carefully controlled financial basis and proper attention should be given to sufficient hours of rest and exercise. In this way the aim of the sanatorium treatment should be to fit the patient both mentally and physically for his post-sanatorium life. Much research is being done at present into the correct assessment by simple and practical methods of the patient's working capacity in order that he may be found work within his powers. Ideally, ex-patients are best employed in the sanatoria or settlements in which they were treated and in which supervision can be continued; when such a course is not possible patients should be directed to special sheltered industries and only those patients who have appeared to have recovered in all aspects should be allowed to enter the open labour market.

Pneumoperitoneum treatment and its reactions.—Aslett and Jarman record 2 fatal reactions after pneumoperitoneum treatment for pulmonary tuberculosis. The treatment appears to be of some value in certain cases but its general value is not yet assessed. (1) A male, aged 32 years, was given 400 cubic centimetres of air followed by refills of 400, 500 and 600 cubic centimetres at intervals of 3, 3 and 7 days. A fourth refill of 800 cubic centimetres was given after 6 days. On the second day after the last refill he became distressed and anxious; there was extreme breathlessness without cyanosis, and then collapse. Oxygen gave a little relief but morphine was more effective, inducing sleep with improvement in pulse and respiration. The patient died 24 hours after the onset of symptoms. (2) A female, aged 23 years, had 13 refills varying from 200 to 600 cubic centimetres. A fourteenth refill of 250 cubic centimetres was followed after 31 hours by slight dyspnoea which became serious in another 24 hours, with distress and some cyanosis. The patient died 4 hours later. The 2 cases are similar in many respects. The signs are suggestive more of cardiac than of pulmonary embarrassment. Pneumoperitoneum treatment carries a genuine risk in advanced cases in which the patients are in poor general condition.

Pulmonary resection.—During the past decade pulmonary resection as a form of treatment for pulmonary tuberculosis has been applied to a steadily increasing number of patients. Overholt and Wilson give a detailed record of 60 resections performed in 2 years. Individual ligation of the hilar structures and the pleural flap method of reinforcing the bronchial closure have eliminated bronchial fistula and empyema as complications of the operation, and improved anaesthesia and chemotherapy have added considerably to the safety of the technique. The authors believe that resection is an effective treatment for patients in good general condition and it saves some of the desperately ill who otherwise are faced by death. It should be a supplementary and not a competitive form of treatment to established methods of rest and collapse therapy. Many of the past failures have been due to improper technique, poor selection of patients, or the removal of too little lung tissue. There are times when tuberculosis, like cancer, must be extirpated at the sacrifice of some functional lung tissue. Resection should not be a last resort but should be used before extension of disease and complications have occurred. The earlier the resection the greater the chance of cure. In the series were 36 pneumonectomies and 24 lobectomies. Contralateral spread is the greatest hazard. Ulceration of the bronchial stump occurred in 8.5 per cent of patients and could be diagnosed only by routine bronchoscopy after resection. It may occur early or late in the postoperative period. Active tuberculosis in the lung to be removed is not a contra-indication to resection; waiting for stabilization of the lesions often robs the patients of their chance to get well. Tuberculous bronchitis is not a contra-indication and neither is a contralateral pulmonary lesion unless it is uncontrollable. The total operative fatality in this series was 11.6 per cent but was only 4.3 per cent in those patients considered to be reasonable operative risks. Choice of patients for operation must of necessity involve varying personal standards of the physicians or surgeons concerned, but there are reasonable indications for operation in those patients with bronchial tuberculosis and stenosis which make pneumothorax or thoracoplasty inadvisable or in those with thick-walled cavities which cannot be collapsed. Similarly those patients who, after thoracoplasty, have positive sputum coming from the operated side may justifiably be operated on, as well as those with extensive productive disease. Resection of the tuberculous lung is usually easier than it is in cases of suppuration or malignancy.

Rest.—Pratt, of the Pratt Diagnostic Hospital, Boston, traces the evolution of the rest treatment of pulmonary tuberculosis. He quotes much interesting historical matter, commencing with the work of Brehmer who, when he asserted in 1853 that consumption was curable, was dubbed a charlatan by Niemeyer. Brehmer's treatment consisted of fresh air and restriction of exercise. His patient and later assistant, Dettweiler, was the pioneer of long hours of rest in the recumbent position and yet failed to realize that rest was the curative agent. Liebermeister was the first to insist, in 1888, that febrile tuberculous patients should be kept in bed at home until they are afebrile before being sent to more favourable climates.

Turban, who published important statistics of 408 patients treated at Davos Platz between August 1889 and June 1896, applied the principle of rest in bed until fever had entirely subsided but prescribed much exercise for afebrile patients. The author thinks that the German, Penzoldt, was the first to apply rest as a treatment *per se* and without exercise, for pulmonary tuberculosis. The first American to recognize that rest was curative was Trudeau who stated in a letter to the author, that he received much abuse in consequence. Pratt traces the gradual acceptance as time passed of this conception and the publication of results by Webb, Emerson, Dunn, Brown, Minor, Kinghorn and many others, and he mentions the advocacy in 1907 at a meeting of the National Tuberculosis Society, of rest in bed continued for several months after subsidence of fever. The author describes his own "tuberculosis classes" for the treatment at home of poor out patients at Massachusetts General Hospital. Weekly meetings were held at which progress was noted and instruction given. Money was given by a rich church parish to cover the salary of a friendly visitor and to buy tents, porches and blankets for the very poor. After 15 years the class was taken over by the Massachusetts State Department of Health. In this treatment rest in bed is the main factor.

Treatment methods in basal tuberculosis—Steen reviews the literature on basal tuberculosis and reports on details of 25 cases found amongst 1,178 tuberculosis patients. Restricted ventilation, which produces impairment of blood and lymph circulation, predisposes lung tissue to tuberculous lesions. Impairment of diaphragmatic movement would likewise favour the development of basal tuberculosis. Women whose breathing is more thoracic in type, have a higher incidence of basal tuberculosis, which is more often seen on the right side because the presence of the liver restricts free diaphragmatic movement. Damage caused by a previous pleurisy or pneumonia may also predispose persons to basal tuberculosis. In one patient who had bilateral pleurisy bilateral basal tuberculosis subsequently developed. The apex of the lower lobe of the lung is a comparatively vulnerable point, at which tuberculosis is liable to develop. Cavitation is frequent in basal tuberculosis, and was found in 9 of the 25 patients. The prognosis in such cases is serious unless the cavity can be effectively collapsed. In the series of 25, progress of the disease was arrested in 13, quiescent in 4, improved in 1 and fatal in 7. Rest in bed is not alone sufficient treatment for basal tuberculosis with cavitation but must be supplemented by collapse therapy. Artificial pneumothorax is usually tried first and such treatment may prove to be satisfactory if pleural effusion is absent. When the lung is adherent to the diaphragm, supplementary phrenic paralysis is indicated and has often proved to be effective. Phrenic nerve paralysis, as an initial procedure in itself, has generally not had favourable results although in 2 cases of the series it proved to be effective. Pneumoperitoneum is a useful form of collapse therapy for basal tuberculosis especially if it is combined with phrenic paralysis, it has proved to be very satisfactory in the few cases in which it has been employed. The best results are obtained when the cavity is situated in the lower third of the lung.

Treatment of complications and symptoms

Analysis of nearly 4 000 post sanatorium histories—Hastings and Behn discuss the post-sanatorium histories of 3,797 tuberculous patients discharged from Glen Lake Sanatorium, Minnesota, between 1916 and the end of 1940. The cases have been divided into three groups: those treated by rest in bed numbered 2 398; those with pneumothorax only, numbered 638, and there were 731 who had other surgical measures with or without pneumothorax. The authors found that the pneumothorax group included a greater percentage of patients with advanced disease than did the non surgical group, but on discharge the percentages of the three groups graded according to arrest of the disease, were 30.7, 45 and 39.8 respectively. Among patients who had died, no statistically significant difference in the average number of years between discharge and death was found in the three groups. In common with other observers Hastings and Behn found that the length of survival varied according to the grade of severity of the disease at discharge. It was found that if a patient had had collapse therapy there was certainly a greater chance of survival whatever the grading of the disease at time of discharge as compared with patients in the unoperated group. Regarding readmissions no and the pneumothorax groups, but those who had other surgical procedures showed a somewhat greater readmission rate. The authors investigated the working capacity of the 2,764 the unoperated group and those who had had a pneumothorax only. If more drastic surgery than a pneumothorax had been necessary, a rather smaller percentage were able to return to normal occupations.

Closure of tuberculous cavities—Loesch explains the different mechanisms by which closure of tuberculous cavities is brought about. That such closure does occur is well recognized but recorded anatomical observations are few in number. The study details 4 cases involving 5 cavities treated by pneumothorax and one patient with one cavity treated by strict rest in bed. A sixth case is described as transitional, the cavity having shrunk markedly under treatment of the patient by strict rest in bed. Before and during treatment the cases are all closely observed radiographically. Serial sectioning of the specimens for histological examination is essential and is carried out in order to obtain a clear picture of the structure and relationship of the bronchi to the obliterated cavities. Lungs are kept passively expanded by the pull of the chest wall. Inspiration produces a greater expansion than does expiration. The bronchi

also participate in this movement. Therapeutic pneumothorax permits the lungs to retract and finally to collapse owing to their elasticity. The mechanism of closure is, for the most part, shrinkage and contraction of the cavity with (1) approximation and final obliteration of the cavity outlet or (2) by fibrotic scar tissue at the point of junction of tuberculous bronchus with healthy tissue or (3) at both these points. The first and second cases detailed are examples of closure by obliteration of the cavity outlet, the bronchus not being tuberculous. The second type of closure is detailed in case 3 in which caseous material extended into the lumen of a large bronchus, filling it out. The fourth case with 2 cavities is an example of closure at both points, fibrotic occlusion at the cavity and caseous occlusion of the bronchus. Occlusion at these points took place before closure of the cavity was complete. No tubercle bacilli could be demonstrated in the inspissated foci, the contents having become partially calcified.

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LUNG DISEASES: MONILIASIS

See also B.E.M.P., Vol. VIII, p. 212.

Differential diagnosis

Radiological differentiation

Added notes on treatment.—Johnston and Heydemann think that pulmonary mycotic infections are usually diagnosed too late and that their recognition is largely the responsibility of the radiologist. They give detailed reports of 8 cases which emphasize the diagnostic difficulties, especially identification by culture. Evaluation of the significance of yeast in sputum is difficult, for it may be primary or secondary, or incidental and of no clinical significance. The radiological differentiation of mycotic from tuberculous infection the authors describe as "not at all reliable". Tuberculosis may develop in a mycotic lung and confuse the picture. Lymph node enlargement and numerous cavities, especially apical, suggest tuberculosis. Cancer metastases are larger and progress more rapidly; primary lesions are usually recognizable. In pulmonary sarcoidosis there may be hilar node enlargement with radiation outward and nodular infiltration and the lesions may be more symmetrical. Skin or mucous membrane conditions may assist in differential diagnosis. Bronchopneumonic lesions are more flame-like and more variable in size. In delayed resolution of pneumonia and chronic fibroid pneumonia there are thick-walled abscesses and more fibrosis. In pneumoconiosis the nodules, usually found in both lungs, are discrete and uniformly distributed, abscess formation is rare and pleural thickening is more uniformly dense. Limitation of diaphragmatic excursion is present in pneumoconiosis but unusual in pulmonary mycosis. In the treatment the authors recommend application of x-rays and administration of very large doses of potassium iodide, 30 grains a day in 3 divided doses, increasing to 120–250 grains a day. If the patient is not allergic to iodides they advise the giving of intravenous sodium iodide daily for 2 or 3 weeks. Johnston and Heydemann go on to state that tuberculosis does not contraindicate the giving of iodides. X-rays they administer once or twice a week over chest and skin lesions, usually not more than 100 r per area treated. They mention that some authors hold that patients with moniliasis and blastomycosis should be desensitized to yeast before they take iodides. Mycotic pulmonary infections, in contrast to tubercular lesions, improve rapidly under treatment.

Johnston, W. A., and Heydemann, J. (1944) *Radiology*, 43, 1.

LUNG DISEASES: TUMOURS

See also B.E.M.P., Vol. VIII, p. 224; and Cumulative Supplement, Key Nos. 992–994.

Malignant tumours of lungs and bronchi

Primary

Treatment of bronchiogenic carcinoma.—Brindley, of the Mayo Clinic, discusses the surgical aspects of bronchiogenic carcinoma and points out that the incidence of this condition is now

second and almost equal to that of carcinoma of the stomach. Of 90 cases in which exploratory thoracotomy was performed, 50 per cent were found to be operable. At x ray examination the lesion was suspected in 80 per cent of the operable cases and in 93 per cent of the inoperable ones. Diagnosis by bronchoscopy was made in 84 per cent of the operable cases and in all of the 36 inoperable cases so examined. Carcinoma of the lung arises from the bronchial mucosa, most often at the hilus and often on the right side. The malignancy is high grade and squamous-celled epithelioma is of slightly more common occurrence than is adenocarcinoma and is better suited for surgical removal since it grows and metastasizes less rapidly. Pre-operatively, the general condition of the patient in the cases discussed was improved as much as was possible and if suppurative disease was present bronchoscopic aspiration was performed. Prophylactic doses of a sulphonamide were given to some of the patients. The incidence of postoperative empyema has been less since sulphonamides have been in use. Intratracheal cyclopropane was the anaesthetic of choice. The posterolateral approach was used in 87 per cent of the operable cases and the anterior approach in the other 13 per cent. Total pneumonectomy with removal of mediastinal lymphatic glands was performed in 43 cases. The immediate mortality was 16 per cent within 24 hours of the operation and 16 per cent at a later period in the hospital. Clagett, commenting on these facts, points out that there is now more interest in carcinoma of the lung. In cases of indeterminate thoracic lesion which suggest carcinoma earlier diagnosis can be achieved by earlier x ray and bronchoscopic examination and if thoracic exploration is more often made, the last procedure is justified on the same grounds as is laparotomy. Pneumonectomy is the most effective treatment available, although it has certain technical difficulties. The patient's general condition should be suitable and the opposite lung and the heart should be sound. Other pulmonary conditions should be excluded as far as is possible and also the presence of metastases, which occur early and widely in lung carcinoma. The prognosis of pneumonectomy has not yet been established so far as the Mayo Clinic is concerned. There is little disability as a result of pneumonectomy so long as the patient does not overexert himself. The surgical mortality is still considerable, but does not compare unfavourably with that of carcinoma of the stomach and the bowel.

Brindley, G. V., Jun (1944) *Proc Mayo Clin*, 19, 361

LUNG DISEASES: GENERAL

Primary pulmonary coccidioidomycosis

Clinical picture

Three stages described—Kunstadter and Pendergrass describe 3 cases of coccidioidomycosis occurring in soldiers who had been stationed in the North American desert areas. The first patient was believed to have had an attack of bronchopneumonia. Fourteen months later x ray examination of the lungs showed multiple nodular lesions. The appearances were similar in the second patient who, 6 months after exposure to infection, complained of cough and chest pain. In the third case no distinction could be drawn between a tuberculous and a coccidioidal cavity. Coccidioidin skin tests were positive in all 3 patients. The authors state that the acute stage of the illness becomes apparent 2-3 weeks after the initial infection. The clinical manifestations consist of fever, bilateral thoracic pain, persistent cough, yellowish brown sputum and haemoptysis. Some patients complain of sore throat and joint pains. A fine macular rash may appear, and there may be erythema nodosum, erythema multiforme, or both. The chest signs are suggestive of acute bronchitis, pneumonic consolidation or pleurisy, in children the disease may resemble primary tuberculosis. The coccidioidin skin test is positive. Blood examination may show an eosinophilia and precipitin and complement fixation tests are likely to be positive in severe infections. The sputum and gastric washings should be examined for fungi. In the subacute stage, cough, chest pain and evening pyrexia are common, but sputum is not abundant and physical findings are usually absent. Many chronic cases are asymptomatic. Routine radiographic examination of the chest, however, may show linear fibrotic markings, thickened pleura or parenchymal infiltrations. Nodular lesions are often seen and these deposits require differentiation from tuberculosis or from metastatic malignant disease. Examination with a magnifying lens shows that the edges of the lesions are serrated. The prognosis is usually excellent, but convalescence may be prolonged and residual lesions may persist.

Diagnosis and differential diagnosis

Modern methods of investigation

Their use in early diagnosis—Wilson states that the correct diagnosis of intrathoracic disease is often delayed for many months owing to insufficient use of modern methods of investigation. In the United States of America advanced disease is present in 60 per cent of the tuberculous patients who are referred to sanatoria. Less than 25 per cent of the patients with cancer of the lung are sent for surgical treatment before the occurrence of metastases or of extension of the tumour. The utilization of mass radiography has served to demonstrate that intrathoracic lesions occur much more often than has been assumed in the past. At first, symptoms may be either absent or very mild. During this stage routine radiography is a valuable supplement to a carefully taken history and a methodically performed physical examination. If physical examination and sputum tests are predominantly employed in cases of pulmonary tuberculosis, the diagnostic efficiency cannot be more than 30 per cent. Routine

sputum smears are unreliable and should be replaced by pooled sputum examined by the concentration method. Many cases require multiple cultures and guineapig inoculation of the sputum and gastric contents. The early diagnosis of pulmonary tuberculosis is of particular importance in young adults, pregnant women, and patients with diabetes mellitus. Tuberculosis and cancer may masquerade as each other or as a variety of diseases such as bronchitis, asthma, pneumonia and lung abscess. Bronchoscopy must be performed on patients suspected of having pulmonary cancer. If bronchoscopy gives negative results, bronchography should be carried out. All patients in whom the biopsy is positive for cancer should be explored, provided that there is no evidence of metastasis or of extension of the tumour. Exploration of the chest can be performed nearly as safely as can an abdominal exploration and with equally satisfactory results.

Kunstadter, R. H., and Pendergrass, R. C. (1945) *J. Amer. med. Ass.*, **127**, 624.

Wilson, N. J. (1945) *New Engl. J. Med.*, **232**, 301.

LUNG DISEASES: PULMONARY EMBOLISM

Treatment

Prophylaxis

Robinson considers that pulmonary embolism may occur in any adult person confined to bed with illness. The condition may complicate inflammation of the veins of the lower extremities. In the prophylaxis of phlebitis it is better to employ exercises than anticoagulant drugs. The patient should be instructed to flex and extend the knee and ankle. Other measures include elevation of the legs twice daily and deep-breathing exercises. It is important to maintain the fluid balance in cases of dehydration with a retarded circulatory rate. Surgical trauma must be reduced to the minimum, but patients should be made ambulatory by the third day after operation. No varicose veins should be injected without a preliminary ligation and division of the great saphenous vein. Moreover, varicose veins should be treated prior to an operation or before the fifth month of pregnancy. Phlegmasia alba dolens and thrombophlebitis of varicose veins rarely give rise to fatal complications because, in these diseases, the thrombus is firmly attached to the vein wall. Most pulmonary emboli result from phlebotrombosis of the deep veins of the leg. Daily examinations of the lower extremities are essential in order to detect the early manifestations of the disorder. Statistics prove that a patient rarely survives more than one embolus ascending from a deep phlebothrombosis. Disaster is prevented either by the surgical removal of emboli or by the ligation and division of the vein above the thrombus. It may be necessary to ligate as high as the inferior vena cava.

Robinson, C. A. (1944) *New Engl. J. Med.*, **231**, 821.

LUPUS ERYTHEMATOSUS

See also B.E.M.P., Vol. VIII, p. 244; and Cumulative Supplement, Key No. 1004.

Aetiology

Pathogenesis

Part played by ovarian hormones.—Rose and Pillsbury describe the clinical and pathological features of lupus erythematosus and review the various theories of its pathogenesis. Since a tuberculous aetiology has not been established, the authors prefer the description, erythematoses. Apart from the local lesions, severe systemic disturbances may occur, including fever, arthralgia, renal lesions, blood dyscrasias, serous effusions and meningitis. Statistical data indicate that there is a striking frequency of both erythematoses and systemic manifestations in females within the active sexual phase of life and that there has been, hitherto, no effective therapy. The authors describe the effects of castration or natural menopause upon the course of the disease in 6 cases, including probably the first recorded use of oophorectomy in treatment. They suggest that the optimal indications for castration are (1) a history of premenstrual aggravation of the cutaneous lesions together with mild systemic phenomena and (2) systemic exacerbations with remissions in women in active menstrual life. A period of remission would obviously appear to be the best time for operation. Evidence is, however, not by any means complete that ovarian hormones play a part in the pathogenesis of erythematoses. Other authors have emphasized the importance of infective-allergic and vasculo-allergic factors. Ovarian hormones may act as sensitizing agents, producing cutaneous vasodilatation or playing an intermediate part in the production of a toxic agent. In a male with erythematoses, investigations have been reported which suggest a decreased 17-ketosteroid: oestrogen ratio and increased hypophyseal gonadotrophic activity. There is obvious need for further knowledge of gonadal function in this syndrome.

Rose, E., and Pillsbury, D. M. (1944) *Ann. intern. Med.*, **21**, 1022.

LUPUS VULGARIS

See also B.E.M.P., Vol. VIII, p. 254.

Treatment

General treatment

Discussion of main principles of therapy.—Airey believes that there is no accurate knowledge of the general incidence of lupus in Great Britain or of the adequacy of its treatment. Improvement should be made by the provision of general and local light therapy for ambulant patients, and by a system of unified control with a central bureau. Gauvain emphasizes that

the general measures usually considered to be necessary for the treatment of tuberculosis are only exceptionally employed in the case of lupus. Local lesions should be regarded as special manifestations of the general disease of tuberculosis. Suspected cases of lupus should be referred to centres, which should be widely distributed throughout the country. As the disease often starts in childhood and as children are very sensitive to the resultant disfigurement, provision should be made for suitable residential treatment with coincident education. This has been done at Treloar's Cripples' Hospital, Hampshire. For severely attacked adults a lupus colony should be established with adequate specialist medical attention. Gauvain has established such a small colony without outside financial help, its great success encouraged further efforts. Burrows believes that small and localized patches of lupus are best treated at metropolitan or similar light centres. Geographical, domestic and financial factors in the past have often hindered the treatment of cases of more extensive disease which need daily general light treatment over a period of months. Treatment in general skin clinics has the advantage that there is a tendency to try new forms of general and local therapy. Burrows discusses the advantages and disadvantages of segregation, and relates that some years ago the London County Council started a special school for children with lupus, but owing to difficulties principally due to the great disparity of ages, were compelled to close it within a year. Since 1901, 4,153 cases of lupus vulgaris have been treated at the London Hospital. It is suggested that the provision of about 10 centres with some residential accommodation would be necessary in England, and that provision should also be made for periods of stay in suitable sanatoria as well as for admission to colonies for the tuberculous. Heaf believes that lupus is a comparatively rare condition and quotes figures to support this. Organization for its treatment is both a medical and a social problem. Treatment is long and costly and should be located in centres each serving a population of 5 000,000. A suggested arrangement is the provision of in-patient treatment in existing non pulmonary tuberculosis sanatoria and hospitals, and out patient treatment in the largest hospital in the area. Heaf estimates there are 10 cases of lupus per million population. Close connexion with medical schools is advisable so that early recognition of the disease may be taught. Extension of the tuberculosis allowances is suggested so that treatment may be followed without financial embarrassment.

Airey, F. S., Burrows, A., Gauvain, H., and Heaf, F. R. G. (1944) *Brit J Derm*, 56, 203

LYMPHATIC VESSELS, DISEASES AND INJURIES

See also B E M P, Vol VIII, p 278

Chylous effusions

Aetiology

Report on two cases—Chylothorax in infancy is the subject of two separate communications, Forbes reporting on an infant 6 weeks old and Wessel on one of 2 weeks of age. (1) The elder infant, whose condition appears to have been complicated by the occurrence of bronchopneumonia, had bilateral chylous effusion and died after 2 months in hospital. Diagnosis of bilateral chylous effusion was not made until one week after admission to hospital. The prominent features on admission were extreme dyspnoea and cyanosis. Treatment of the condition resolves itself into repetition of thoracentesis governed by the degree of dyspnoea and cyanosis displayed by the infant. Thoracentesis is necessary, as a rule, every 24 hours. Observations are made on the absorption of vitamins A and D and on the effects of restoring the chylous effusion to the venous system. Attention is drawn to the difficulty of maintaining nutrition in these cases in which large quantities of chyle, rich in fat and protein, are lost in the aspirated effusion. In Forbes's case no ill effects were observed from the introduction of the aspirated chyle into the veins. For the bilateral chylothorax, oxygen was administered continuously, and plasma and whole blood transfusions were given as well as dextrose and other stimulating solutions. In spite of these measures the infant's condition deteriorated, 300 grammes of body weight being lost during her stay in hospital. Observations of vitamin A absorption indicate that after oral administration the concentration of the vitamin in the chyle rises rapidly. With carotene in addition the vitamin A content of the chyle is not increased. Administration of vitamin D orally proves that it is absorbed in a fourfold amount after 4 hours and fortyfold after 6 hours. Necropsy revealed no cause for the chylous effusion. (2) In the younger infant, who had a right sided chylothorax and recovered spontaneously after 14 days, the onset of a watery diarrhoea coincided with a lessening of the chylous effusion. The diet was low in fat and high in protein, 10 grammes of extra protein being added to the skim milk. A vitamin A absorption test was made, which showed delay in absorption. Vitamin A was present in the chylous fluid, both in the fasting sample and in the 24-hour sample.

Forbes G. B. (1944) *J Pediat*, 25, 191

Wessel, M. A. (1944) *J Pediat*, 25, 201

LYMPHOPATHIA VENEREUM

See also B E M P, Vol VIII, p 287, and Cumulative Supplement, Key No 1017

Aetiology

Causal organism

Experiments on the chicken embryo—Shaffer, Jones, Grace, Hamre and Rake used yolk sacs of developing chicken embryos for isolating the causal agent of lymphogranuloma

venereum. It has been recently shown that the agent is one of a large group causing natural infection, overt or latent, in many species of animal. Furthermore, these other agents display antigenic similarities to the agent of lymphogranuloma venereum and are morphologically difficult to distinguish; some of them are susceptible to the sulphonamides. Conclusions drawn from results of animal passage of human lymphogranulomatous material may therefore have been fallacious and the agent isolated is not certainly that responsible for the human infection. Although one agent causes infection in chickens no investigator has recorded transmission of infection through the egg. Apparently the chicken embryo, protected within the shell, is immune from any but a deliberately introduced agent. It was therefore used in the authors' investigations for inoculation by the yolk sac route. By this method two strains of the agent of lymphogranuloma venereum have been isolated from suspensions of pus from human inguinal buboes without the possibility of contamination by related agents which exist in a latent stage in the animals used. Therefore the strains which have been isolated in the past may not represent the true aetiological agent of the human disease since hitherto the lymphogranuloma-psittacosis group of agents have never been described as spontaneous infectors of the fertile chicken egg.

Shaffer, M. F., Jones, Helen, Grace, A. W., Hamre, Dorothy M., and Rake, G.
(1944) *J. infect. Dis.*, 75, 109.

MALARIA

See also B.E.M.P., Vol. VIII, p. 304; and Cumulative Supplement, Key Nos. 1018 and 1019.

Aetiology

Epidemiology

Strain of parasite and immunity.—Taliaferro reviews the factors concerned in natural and acquired immunity to various avian, simian and human malarias. Almost all human beings have some natural immunity to the parasite and certain races have a higher immunity than have others. Acquired immunity in the human disease is to a large extent strain specific. *Plasmodium vivax* probably contains the most numerous immunologically different strains and *Plasmodium malariae* the least. Some malarias give a more solid immunity than do others. *Plasmodium falciparum* generally either kills the host or results in good clinical cure, whereas patients with *P. vivax* and *P. malariae* infections usually recover but suffer relapses of varying degrees of severity. Natural and acquired immunity is bound up with the death rate of the parasites and their removal from the circulation by a phagocytic process in which the macrophages of the spleen, liver and bone marrow are chiefly concerned. New macrophages may arise homoplastically from pre-existing macrophages and heteroplastically from lymphocytes and monocytes. The process is sluggish in natural and intense in acquired immunity and is preceded by the filtration of parasitized erythrocytes which occurs notably in the Billroth cords of the spleen and is due probably to specific agglutination and opsonification. The latter also affects the free parasites in acquired immunity and may explain why it can be passively transferred with immune serum in *Plasmodium knowlesi* infections in the rhesus monkey. Active immunization without infection has failed in experiments in monkeys but a partial immunity has been produced in chickens with sporozoites of *Plasmodium gallinaceum* obtained from the mosquito and inactivated by the application of ultra-violet light.

Treatment

Prophylaxis and cure

Mepacrine hydrochloride and pyrethrum.—McCoy discusses malaria in wartime, its treatment and control, and post-war precautions. In tropical warfare malaria has claimed more casualties than have bombs and bullets. Lessons have been learned from wartime experiences. The supply of quinine was cut off after the occupation of Java by the Japanese. Atabrine (mepacrine hydrochloride), a drug obtained from researches started in Germany during the war of 1914–1918, has proved to be an effective substitute and in military operations is even preferable to quinine. Neither drug is a true specific in malaria; the ideal antimalarial has not yet been found but there is hope of its discovery. Atabrine must be given in large initial doses in order to produce a prompt clinical response. As a prophylactic given over a period it does not prevent infection, but it does prevent the development of malignant tertian malaria, thus reducing the death rate. For control of the disease, breeding places, especially at base installations, are drained, filled up and sprayed with larvicides. In the battle area, troops must rely on personal protective measures: use of mosquito net, repellent substances, sprays and protective clothing. The "mosquito bomb", one pound in weight, contains enough pyrethrum insecticide to kill mosquitoes in an area of 150,000 cubic feet. D.D.T. (dichlorodiphenyl-trichlorethane) kills larvae and adult mosquitoes and will have far-reaching effects in the control of malaria. Probably 80 per cent of the troops will be entirely free from malaria when they are discharged from the Army. It will be essential to prevent the importation by airborne transport or by infected persons of anopheline species into malaria-free areas.

Spray-killing by pyrethrum.—Edey describes the conduct of large-scale spray-killing anti-mosquito measures practised from November 1942 to November 1943 at Takoradi, Gold Coast. A total of 637,811 units, each comprising 1,000 cubic feet of room space, were sprayed and swept during this period by organized native labour under a European superintendent. A direct relationship was demonstrated between mosquito prevalence and rainfall and be-

tween anopheline predominance and rainfall. Initially, all zones were treated with a standard 1 in 160 cresol-kerosene mixture, dispersed with domestic hand-pumps. Later, selected zones were treated with either dry pyrethrum, pyrethrum kerosene or pyrethrum aerosol, the latter being produced from Westinghouse dispensers. Detailed comparison of the insecticidal methods indicates that, in terms of labour economy, pyrethrum aerosol is best, pyrethrum kerosene ranking next. The comparative costs incurred in using the insecticides, excluding dry pyrethrum, were analysed in terms of house room and population units. By either method the spraying cost amounted to little more than one penny per head per week. In the area sprayed, the total malaria incidence among the two main groups of European service staff in 1943 was respectively 42.7 and 34.2 per cent of the 1942 figures, whereas the general malaria rate in the services throughout the Gold Coast showed only a 50 per cent fall, comparatively. Although country-wide measures such as screening and mepacrine prophylaxis were partly responsible for the reduced incidence in Takoradi, the purely local spray-killing measures were evidently a valuable contribution. There is less specific evidence of the benefits derived by the non-European population, but one of the tables of figures shows that, as far as infants are concerned, those living within the control and spray-killing zones were considerably freer from malaria parasites than were infants living outside such zones. The keeping of comprehensive spray killing statistics afforded indirect assistance to other locally practised control measures by supplementing the "catching station" records. Eddey concludes that a spray-killing scheme should be an integral part of any emergency antimalaria measure.

Cure

Treatment of the relapse—Manson Bahr describes the treatment of malarial relapses, which at present are being commonly encountered. He emphasizes that benign tertian malaria is characterized by tendency to frequent relapse, is by no means a tropical disease, has wide geographical distribution and during summer flourishes in temperate zones. Subtertian malaria does not produce relapses as incapacitating. The assertion that blood examinations are useless except during febrile periods the author thinks is fallacious, moreover pathologists cannot be expected to identify parasites in the blood of patients who were adequately treated before films were taken. Stating that "the effects of quinine poisoning are more intolerable than those of malaria", the author condemns heroic dosage. He limits the dose of soluble salts such as the hydrochloride to 30 grains a day for 3 or 4 days. The sulphate should be dissolved by addition of sulphuric acid, if it is possible to prevent it, it should not be administered as pills, especially as sugar-coated pills, since these, if they are kept for long periods in stoppered bottles in hot countries, may become insoluble. Failure to realize this possibility has caused fatalities. Achlorhydria, common in malarial attacks, may diminish quinine absorption. Intravenous injection, in doses never larger than 10 grains and in at least 10 cubic centimetres of isotonic saline, should be reserved for severe subtertian forms. Describing unpleasant results of intramuscular injections of acid salts of quinine the author advocates Solvochin, a 25 per cent solution of quinine at a hydrogen ion concentration of 7.2 in phenyl-dimethylpyrazolone (phenazone), 2.2 cubic centimetres of which contain $7\frac{1}{2}$ grains of quinine. The synthetic antimalarial drugs are mepacrine hydrochloride—cumulative in action and specific especially against the subtertian parasite—and pamaquin, a quinoline derivative. For anti relapse treatment of benign malaria Manson Bahr advocates pamaquin $\frac{1}{2}$ grain, with $7\frac{1}{2}$ grains of quinine hydrochloride for 7 days, a 4-day interval, and then a repetition of the course. This sequence can be given four or five times if it is well tolerated. For anti relapse treatment of subtertian malaria the treatment is 2 injections of 2 cubic centimetres of Solvochin daily for 4 days and mepacrine hydrochloride $1\frac{1}{2}$ grains 3 times daily with 10 grains of quinine hydrochloride for 7 days by the mouth, a 5-day interval and then a repetition of the mepacrine and quinine course on two separate occasions with a weekly interval.

Mepacrine hydrochloride—Shannon and his colleagues present data on the pharmacological action of atabrine (mepacrine hydrochloride) in the treatment of malaria. The observations are based on the fundamental premise that the antimalarial action is related to the concentration of the drug in the plasma. A true value for this concentration can be obtained only after careful separation of the plasma from the leucocytes, because these cells concentrate the drug at a relatively high level. Moreover, diffusion of the drug from the leucocytes must be reduced to the minimum. The absorption of atabrine from the gastro-intestinal tract is rapid and complete. The drug is degraded gradually, the rate of excretion is low and there is a tendency to extensive localization in many organs. These facts account for the progressive accumulation of the drug in the body after doses of 0.4 or 0.6 gramme repeated at weekly intervals. Low plasma concentrations are often observed during the early phases of treatment. Rapid alleviation, therefore, of the symptoms of malaria is not to be expected with a dosage of 0.1 gramme given 3 times daily. The dosage should consist of 0.8 gramme on the first day, this dose may be repeated on the second day after which 0.3 gramme should be given daily. It is often advisable, however, to give part of the initial dose by a parenteral route, as in the case of patients with dysentery or in those in whom diarrhoea develops after taking large doses of the drug by the mouth. In these patients an attack of diarrhoea is likely to limit absorption from the gastro-intestinal tract. Parenteral administration enables adequate concentration to be maintained in the plasma but prolonged use of the method is rarely warranted. Intravenous therapy is not advisable owing to the severity of the reactions, intramuscular injections are to be preferred.

Eddey, L. G. (1944) *Trans. R. Soc. trop. Med. Hyg.*, **38**, 167.

Manson-Bahr, P. (1944) *Med. Pr.*, **212**, 342.

McCoy, O. R. (1944) *Science*, **100**, 535.

Shannon, J. A., Earle, D. P., Jun., Brodie, B. B., Taggart, J. V., Berliner, R. W., and the Resident Staff of the Research Service (1944) *J. Pharmacol.*, **81**, 307.

Taliaferro, W. H. (1944) *Amer. J. clin. Path.*, **14**, 593.

MATERNAL MORTALITY

See also B.E.M.P., Vol. VIII, p. 394; and Cumulative Supplement, Key No. 1026.

Causes of maternal mortality

Haemorrhage

Infection and haemorrhage in pregnancy and childbirth.—Blair comments on the causes of mortality in pregnancy and childbirth. Maternal deaths in Vancouver have decreased, especially in the last 10 years. Analysis of the causes of death shows that in the rate of mortality due to infection there is a decided improvement, in that due to toxæmia a minor improvement and in that due to haemorrhage scarcely any improvement. As regards infection, hospitals, better equipment and technique and powerful chemotherapeutic drugs have played their part in reduction of deaths. Better antenatal care tends to reduce the number of cases of toxæmia. An analysis of 3 years' admissions to Vancouver General Hospital gives the following figures: (1) 7 deaths in 1,492 abortions, (2) 13 deaths in 9,876 viable pregnancies and (3) one death in 78 ectopic pregnancies. In the first group, 5 died from infection and 2 from haemorrhage. In the second group, 5 died from haemorrhage and none from sepsis. In the author's experience the chief cause of maternal death before viability is infection and after viability haemorrhage. Only when the maternal pulse is 100 or less with no sign of shock or haemorrhage can the obstetrician feel that his patient is safe. Two cases are described in which profound shock with collapse of veins developed so that no intravenous restoratives could be given; both patients died. It is now a rule in the Hospital that every patient whose pulse reaches 120 and contact with whose doctor cannot at once be established shall immediately receive intravenously 5 per cent glucose in sterile water. Infusions into the bone marrow—of the sternum in adults and of the tibia in infants—are practised so that, should the venous system collapse as in the 2 cases mentioned, blood, saline or plasma can be administered.

Prevention of maternal mortality

General measures

Statistics of 3,457 cases.—Cummings observes that puerperal sepsis still causes about half the number of maternal deaths in the United States of America. The hazards of endogenous sources of infection may be reduced by bringing the patient to term in optimum physical condition. Exogenous infection may be lessened by careful aseptic and antiseptic technique, by careful preparation of the patient, by the wearing of masks over nose and mouth, and by the exclusion of attendants who may be carriers of virulent bacteria. Cummings describes the routine used in the maternity department of the Evanston Hospital, Illinois, in which, during the past 3 years, 3,457 patients were delivered; the corrected maternal morbidity rate was 3.64 per cent. One hundred and twenty-four patients had an average of 3.7 days with temperatures of 100.4° F. or over. Analysis showed that Caesarean section, packing the uterus and manual removal of the placenta carried the highest morbidity rates. Excluding low forceps deliveries, the morbidity for cases delivered operatively was 14.98 per cent. Those delivered with low forceps had a slightly lower morbidity rate than had those delivered spontaneously. Artificial rupture of membranes for induction of labour caused no increased morbidity. Loosening of the membranes was associated with increased sepsis. The morbidity rate increased slightly during months when upper respiratory infection was common. The prevention of puerperal sepsis is the responsibility of the physician. After proper prenatal care, the prime essentials are meticulous aseptic technique throughout labour, delivery and the puerperium, and sound obstetric management, so that unnecessary major operations, carrying increased likelihood of infection, may be avoided. Undue reliance should not be placed on methods of antisepsis or on the employment of sulphonamide drugs, however therapeutically useful these may be.

Blair, M. (1945) *Canad. med. Ass. J.*, **52**, 166.

Cummings, W. G. (1945) *Amer. J. Obstet. Gynec.*, **49**, 409.

after the fourth injection and in twin children attenuated measles developed 14 days after the start of the inoculations, the remaining 36 members of the group remained free from infection. Bloxson comments that the small dosage and the great protection afforded suggests that an active immunity was produced. The small dosage of the method has economical advantages. Stillermann and Thalmer are quoted as stating that, in an epidemic in 1941 in New York, the secondary attack rate in susceptible contacts aged up to 14 years was 75 per cent. Thus in the group of 40, measles might have been expected to develop in 30. It is suggested that the serum of recently convalescent measles patients, within a week of the cessation of the fever and the rash, may contain enough attenuated virus to act as antigen to provoke the development of an active immunity when it is given according to the method described.

Bloxson, A (1945) *J Pediat*, 26, 32

MEGACOLON AND ANAL ACHALASIA

See also B E M P, Vol VIII, p 470, and Cumulative Supplement, Key No 1031.

Treatment

Non-operative

Management and prognosis—Grimson, Vandegrift and Dratz discuss the management and prognosis of megacolon or Hirschsprung's disease, a comparatively rare disease of unknown aetiology and therefore difficult to treat. The authors describe 24 cases of well established megacolon which have been treated at Duke Hospital, Durham, North Carolina, since 1930. The cases are divided into three groups (1) 12 cases with uniform and at all times immense dilatation of the whole colon and rectum, (2) 7 patients with great dilatation of the proximal colon and rectum and (3) 5 patients with enormous dilatation of the sigmoid and descending colon and variable involvement of the proximal colon of the rectum. All patients in group (1) received routine medical treatment, namely special diet, laxatives, enemata and parasympatheticomimetics. Eight patients did well, one still has troublesome symptoms. 2 received surgical treatment for volvulus and one died 3 years after sympathectomy. The authors conclude that this type do well on medical treatment provided that there is no persistent distension and that nutrition is adequate. In group (2), 4 patients had medical treatment and one had a sympathectomy as well, all these patients died. Three are still living after a one-stage resection of the megacolon with ileosigmoidostomy. Grimson and his colleagues believe that in this type treatment by colostomy or resection of the megacolon gives the best prognosis. In group (3), all 5 patients are living, 2 being free from symptoms. Three had manifestly dilated rectums, and in one the rectum dilated during observation with consequent relief of symptoms. All had medical treatment only. The authors conclude that the prognosis is best when the rectum is dilated as well as the colon, and that medical treatment alone may be sufficient although surgery may become necessary as an emergency or for great and persistent distension.

Grimson, K S., Vandegrift, H N., and Dratz, H M (1944) *Amer. J Dis Child*, 68, 102

MENINGITIS

See also B E M P, Vol VIII, p 495, and Cumulative Supplement, Key Nos 1033-1040

Tuberculous meningitis

Course and prognosis

Tuberculomata in the nervous system—Jennings records 2 cases of recovery from tuberculous meningitis—a comparatively rare occurrence. In neither case was there a family history of tuberculosis. One patient was infected with human tubercle bacilli of low virulence, a condition which was confirmed by culture and typing. The cerebrospinal fluids of both patients contained tubercle bacilli and other evidences of meningitis. Clinically there was headache, vomiting, fever and neck rigidity. Kernig's sign was absent in one patient and was present in the other, who had pronounced ocular signs. The headache and other signs were much improved after initial lumbar puncture, which was repeated twice in one case and 5 times in the other. One patient is known to have remained well for more than a year, but trace of the other has been lost. Few cases of recovery from tuberculous meningitis have been reported and of these some had tubercle bacilli in the cerebrospinal fluid but had not shown small tuberculomata in the nervous system which had healed without causing meningitis. According to other observers these tuberculomata are found to exist, preceding the onset of meningitis, in the great majority of patients who die of tuberculous meningitis.

Syphilitic meningitis

Treatment

Acute condition treated by penicillin—Nelson and Duncan describe in detail the penicillin treatment at the Johns Hopkins Hospital of 10 cases of acute syphilitic meningitis. With the exception of 2 cases, in regard to which the duration of the infection was not known, no patient had had syphilis for longer than 20 months. Four patients had received no previous treatment for syphilis and of the others only one had had an adequate course of treatment. Only one patient had had a previous course of penicillin, having received in all 60,000 units, a total dosage now thought to be inadequate. In the series described, treatment lasted 7½-11

days, and total dosages of 600,000–4,000,000 Oxford units of penicillin were given by intramuscular injection. It was assumed that in early neurosyphilis it is sufficient for the chemotherapeutic agent to penetrate the affected tissues without necessarily penetrating into the cerebrospinal fluid. The results achieved by treatment carried out along these lines suggest that such a supposition is correct. The patients in the series all remained in touch with the hospital for periods varying from 104 to 310 days from the beginning of treatment and during the time no clinical relapse occurred although one patient showed relapse in the cerebrospinal fluid findings. The immediate clinical and laboratory response to treatment was excellent. Headache and neck rigidity disappeared in 2 days and in all except one case cranial nerve palsies disappeared within 98 days. In 3 cases, the blood serological reaction became negative and in others the titre was falling towards negative. A sudden fall in the cerebrospinal fluid cell count occurred in all cases immediately after therapy and in all except one the count became normal during the observation period. Improvement also occurred in the protein content and Wassermann reactions of the spinal fluid. The mastoc curve, abnormal in all cases except one, improved in every instance and became normal in 5. The authors advise that acute syphilitic meningitis should be treated by 3-hourly or 4-hourly intramuscular injections of penicillin, with a total dosage of 2,000,000–3,000,000 units over a period of 8–16 days. Careful clinical and laboratory examinations should subsequently be made at 3-monthly intervals for the first year, 6-monthly for the next 2–3 years and thereafter at yearly intervals.

General

Occurrence of glycosuria

Theories of origin.—Ferguson and Barr review 30 cases of glycosuria in 72 patients with meningitis. Fourteen of these patients had received infusions of dextrose solution, and in three cases the past histories and sugar tolerance curves indicated the presence of diabetes mellitus or a prediabetic state. In the remaining cases the cause was undetermined. Spontaneous glycosuria was found in over one-third of 26 cases of meningococcal meningitis and less often in pneumococcal, tuberculous and staphylococcal meningitis. The glycosuria occurred at the onset of the illness and was transient, disappearing by the third day in the majority of cases. The condition was accompanied in many instances by hyperglycaemia and diminished tolerance to sugar. Ketosis, with or without glycosuria, was often present. It is considered to be unlikely that all of those who had sugar in the urine were in a prediabetic state because their number was much greater than would be expected from the known incidence of diabetes mellitus. There is no evidence to support the theories that the glycosuria was due to depression of insular function, excessive hepatic glycogenolysis or inhibition of the action of insulin. It is true that insulin therapy caused the prompt removal of glycosuria but disappearance was equally prompt when no insulin was given. The presence of cranial nerve paralyses may support the theory that the process is allied to the *piqûre* diabetes of Claude Bernard. Cases of meningitis are recorded, however, in which glycosuria appeared before there were any signs of meningeal involvement. The possibility exists that the glycosuria was the result of an exaggerated response to a sudden severe infection. A practical outcome of the investigation consists in the fact that the acidosis of diabetes mellitus may be diagnosed in error when coma with glycosuria and ketosis occur at the onset of meningitis.

Ferguson, F., and Barr, D. (1944) *Ann. intern. Med.*, **21**, 173.

Jennings, G. H. (1945) *Lancet*, **1**, 466.

Nelson, R. A., and Duncan, L. (1944) *Johns Hopk. Hosp. Bull.*, **75**, 327.

MENORRHAGIA AND METRORRHAGIA

See also B.E.M.P., Vol. VIII, p. 508; and Cumulative Supplement, Key. Nos. 1041–1043.

Menorrhagia

Treatment

Progesterone therapy in metropathia haemorrhagica.—Scowen outlines the events which had led to the isolation of progesterone, beginning with the early observations of Born and Fraenkel and Loeb on the corpus luteum and the discovery by the last-named that deciduomata could be produced in the guineapig only during the luteal phase of the cycle. Bouin and Ancel later demonstrated that progestation proliferation was dependent upon the corpus luteum, but faulty interpretation of growth changes in the uterus—now known to be dependent upon the oestrogenic hormone—confused knowledge of the specific action of the corpus luteum hormone on the endometrium. From experiments first conducted by Corner, it later became evident that corpus luteum hormone could exert its effect only on a uterus previously sensitized by oestrogenic substance. In 1929 Marrian found an inactive alcoholic substance in the urine of pregnant women, pregnanediol, which is probably an excretion product of progesterone. The latter was isolated in pure crystalline form in 1934. A compound of pregnanediol is present in the urine during pregnancy and the luteal phase of the cycle. Subsequent investigations of metropathia haemorrhagica showed there to be absence of pregnanediol over many months. Progesterone was therefore applied as substitution therapy and usually fresh bleeding or intensification of previous bleeding occurred which ceased spontaneously after a few days. Relapses occurred unless injections of progesterone were given daily. It is now possible to control metropathia haemorrhagica by these means and recovery

occasionally occurs without continuation treatment. More recently anhydrohydroxy-progesterone (ethisterone, pregnenolone) has been discovered which has progestational activity when given orally, but its activity, weight for weight, is only about one-tenth that of progesterone and the relapse rate is high when it is used in the treatment of metropathia haemorrhagica. Progesterone produces secretory endometrium but not full conversion, and this does not occur even when large doses of oestrogen are given in order to prepare the uterus for the action of progesterone.

Limitations of radiology—Meigs discusses uterine bleeding in relation to radiology. Abnormal uterine bleeding is perhaps the commonest abnormality of the menstrual cycle and it is important to find the cause before the complaint is treated. Meigs describes the constitution of menstrual blood, pointing out that variations in its components may cause abnormal bleeding, as for example when a deficiency of calcium or blood platelets prevents normal clotting. Consequently certain blood dyscrasias such as leukaemia or thrombocytopenic purpura may show abnormal uterine bleeding. The menstrual cycle is under hormonal control and Meigs points out that bleeding can be produced in a castrated patient when oestrin or progestin (progesterone) is omitted from treatment. The sympathetic nervous system also appears to exercise some control over the uterus since anger or fright can precipitate the menstrual flow and bleeding will start a day or so after presacral neurectomy. The commonest type of abnormal bleeding caused by hormonal imbalance is metropathia haemorrhagica, which can be treated by the administration of corpus luteum hormone or progestin. Oestrin producing tumours as well as deficiencies of vitamins C, K, and possibly B, may cause abnormal bleeding and cervical or endometrial polypi, fibroids, ovarian cysts and carcinomata of the reproductive system too may be responsible. Before any treatment is ordered, a diagnosis of the cause of the bleeding should always be made and patients, particularly those past the menopause, should never be given radium or x-ray therapy prior to a diagnostic curettage or biopsy, because such therapy by stopping haemorrhage may mask a carcinoma until the condition has become inoperable. In benign bleeding Meigs believes that total hysterectomy leaving the ovaries intact is always preferable and that x-ray therapy should be reserved chiefly for those cases in which the general health prevents surgical interference and for spinsters near the menopause.

Meigs, J. V. (1944) *New Engl J Med*, 231, 549.

Scowen, E. F. (1944) *Proc R Soc Med*, 37, 677.

MENTAL DEFICIENCY

See also B E M P, Vol VIII, p 520, and Cumulative Supplement, Key Nos 1044-1056

Clinical types

Phenylpyruvic oligophrenia

Urinary signs—Medlicott describes a rare form of mental deficiency, phenylpyruvic oligophrenia, of which 2 cases were found in Porirua Mental Hospital, New Zealand, among a total number of 190 mentally deficient patients. Phenylpyruvic oligophrenia (Follings's disease) is a form of mental deficiency associated with a defect in the metabolism of an aromatic amino acid, phenylalanine, in which its normal katabolite, phenylpyruvic acid, is not oxidized but is excreted in quantity, unchanged, in the urine. Its presence is shown by the formation of a dark green colour which soon fades on the addition of a few drops of ferric chloride (5 per cent) to acid urine. Both sexes are equally affected and the condition frequently occurs among several members of the same sibship. It appears to be genetic in origin, being carried by a rare recessive gene. The metabolic defect may be due to lack of an oxidative enzyme, and as it has been found to be accompanied by lowered utilization of oxygen and glucose by the brain, a similar enzyme defect may produce the mental deficiency and the neurological accompaniment. The disease usually occurs in blonde blue-eyed types, with delicate skin, regular features and comparatively well formed body. The mental defect is one of development and is usually severe: the patients being idiots or imbeciles. The neurological symptoms are extrapyramidal in character. Deep reflexes are always exaggerated, and there may be clonus. Other reflexes are normal, as are the cranial nerves and the cerebrospinal fluid. There may be tremors and athetosis, sometimes with choreic movements. The posture in the lower grade defectives is usually one of general flexion, the patient walking with short steps and holding the body rigid. Photosensitivity is often marked: patches of eczema are present in many cases, as well as acrocyanosis. Puberty occurs late, but is normal, the external genitalia are usually normally developed, and one phenylpyruvic idiot is reported to have borne a child.

Medlicott, R. W. (1944) *N Z med J*, 43, 191.

MENTAL DISEASES, HEREDITY

See also B E M P, Vol VIII, p 552, and Cumulative Supplement Key Nos 1057-1061

Prognosis of inheritance

Changes of inheritance

Learning ability of young rats suckled by mothers treated prenatally with sodium bromide—Previous observers have shown that in rats there is a relationship between the amount of intact cerebral area and maze-learning and that rats suckled during the early days of life by mothers deficient in thiamine (aneurine) hydrochloride or riboflavin give subnormal

performances by this test. Harned, Hamilton and Cole have studied the effect of prenatal administration of sodium bromide on maze-learning ability. The rats were divided into four groups. The controls were offspring of normal mothers and the three experimental groups came from mothers dosed with 40, 80 and 120 milligrams of sodium bromide. After birth the young rats received no bromide except that obtained from the mothers' milk. All of them were weaned not later than the twentieth day. With hunger as the motivating factor and food as the incentive, the rats were tested in a U-shaped maze with 5 *culs-de-sac*; the animals were between 61 and 85 days of age and at this time were free of abnormal amounts of bromide. The group which received the largest dose of bromide was significantly slower in learning than were each of the other groups, but the latter did not differ among themselves. All groups reached the same level of performance before the twenty-fifth day of the test, a fact suggesting that in the maze test the deleterious effects of the bromide appear in the rate of learning rather than in the performance finally attained. Maier has shown that there is a significant correlation between the extent of cerebral lesions and the scores with his 3-table test for reasoning, and other workers have shown that there is a relationship between magnitude of cerebral lesion and errors in maze-learning.

Harned, B. K., Hamilton, H. C., and Cole, Versa V. (1944) *J. Pharmacol.*, 82, 215.

METABOLISM

See also B.E.M.P., Vol. VIII, p. 581; and Cumulative Supplement, Key No. 1070.

The energy exchanges of the body

Influence of hormones and drugs

Acid and alkaline phosphatase.—Wachstein investigates the behaviour of histochemically demonstrable alkaline and acid phosphatase activity in kidneys damaged severely by choline deficiency in the diet. Young rats were fed on various diets for 10–15 days and were then killed. The greatest incidence of renal necrosis was in the group fed on fibrin as the source of protein. The kidney in the acute phase of choline deficiency was enlarged with the outer surface dark red. There was extensive necrosis of the tubules in the cortex. The majority of the glomeruli showed no change. Staining reactions for alkaline phosphatase activity appeared in the proximal convoluted tubules with no staining of the distal convoluted and collecting tubules. There was indicated a varying amount of alkaline phosphatase activity in the medullary capillaries and in the glomeruli. With acute choline deficiency there was marked reduction of alkaline phosphatase activity in the convoluted tubules. With subacute deficiency, glomeruli showed strong phosphatase activity which was also pronounced in the afferent vessels and in the interlobular arteries in the cortical region with a reduction of phosphatase in the convoluted tubules. The staining for acid phosphatase was much more pronounced in the cortex than in the medulla. With acute choline deficiency there was marked diminution of acid phosphatase activity in the cortical tubules, most distinct in the outer portion of the cortex but less extensive than for alkaline phosphatase. This method of examination can determine the site and the intensity of cellular enzymatic activities and will open a new approach to the study of cellular activity in health and disease.

Metabolism of food constituents

Protein metabolism

Effects of fractures and operations.—Howard and his colleagues discuss nitrogen metabolism after skeletal fractures and operations on bones of adults. Six healthy males with fractures of the lower extremities treated in casts and 3 patients with operations on the femur were studied, as well as one of the first 6 patients who subsequently had had a herniorrhaphy. Nitrogen balance studies were started immediately the patients were well enough to allow accurate collection of urine and faeces. Diets were very carefully controlled. In all the fracture cases there was considerable loss of nitrogen. Estimations did not start until on the average 3·3 days after injury and, correcting for this, the authors state that the average loss of body nitrogen was over 220 grammes, equivalent to 1,400 grammes of protein or 15 pounds of muscle protoplasm. The peak of the nitrogen loss was 5·6 days on the average after injury, nitrogen equilibrium not being established for approximately 35 days, and recovery of the nitrogen loss was slow. In the case of the 3 operative cases and the one of herniorrhaphy the nitrogen loss was less, averaging 46 grammes, and the peak occurred on the fourth day; in contrast to the others these patients rapidly regained their nitrogen losses. Discussing the nitrogen loss Howard and his colleagues do not believe that atrophy occasioned by disuse could account for it since the factor was equally present in the operative osteotomy cases. They also do not believe that anaesthesia, fever, infection or the administration of sulphonamides can account for the major part of the nitrogen loss. The authors state that the relation between the protein losses and the calorie and protein contents of the diets of the patients is of great interest. The diets were for the most part above the normal standard for healthy adults, and during the stage of protein loss no patient complained of being inadequately fed.

Fat metabolism

Metabolic errors in children.—Allen discusses some of the common errors of metabolism in children. He points out that the management of the diabetic child is particularly difficult because transgressions in diet are very liable to occur and also because the dosage of insulin must be relatively large since calorie intake must cater for normal physical development as well as for maintenance of nutrition. The outlook for such children is not good. Again, certain

children suffer from the effects of having a slight tolerance for fats. In infancy this manifests itself only in bottle fed babies, the vomit is sour and rancid and there is a diarrhoea which excoriates the buttocks. Unlike enteritis, this condition rapidly responds to a decrease in fatty diet and is not accompanied by pyrexia, toxæmia or dehydration. Fat intolerance in childhood causes attacks of diarrhoea and vomiting and is generally found in the characteristically 'lean' type of child whose overanxious mother is constantly trying to fatten him. An intake decreased in fat and increased in carbohydrate effects a cure. Other children, of the mentally bright and physically active type, have an inborn inability to store glycogen. They become hypoglycaemic and suffer from exhaustion, headaches and vomiting. This type, also, is often misguidedly given a diet rich in fat and is deprived of carbohydrates, a reversal of these two constituents of the diet cures the condition. Difficulty in storing minerals and vitamins is sometimes encountered and the results of treatment in such cases is not always encouraging. A diet rich in dairy products and the requisite minerals and vitamins is, however, an essential in treatment.

Mineral metabolism

Effects of drinking sea water—Elkington and Winkler describe the physiological effects of drinking undiluted sea water. Recorded clinical accounts all describe central nervous system and mental disturbances, suicide attempts are common. Dogs exhibited tremors, hyperactive reflexes, motor incoordination and finally irregular and failing breathing. Circulation continued good without the diminution of plasma volume commonly seen in peripheral vascular collapse. Pulse remained vigorous and electrocardiograms were normal. Experiments have proved that ingestion by human beings of sodium chloride solution of greater concentration than that of human urine tends to dehydration and hypertonicity of body fluids. Various investigations have demonstrated an important difference between the early and late distribution of the dehydration resulting from continued ingestion of hypertonic saline solution. In early stages all the sodium chloride is excreted fairly quickly with some loss of body water, later, however, as dehydration progresses, body fluid is less readily sacrificed and sodium chloride is retained and thus extracellular fluid is maintained at the expense of intracellular fluid. In the late stages as observed in shipwreck victims and in dogs, the extracellular fluid volume is apparently maintained at the expense of severe intracellular dehydration. The effect of this dehydration on the cells of the central nervous system would explain the clinical manifestations since there is, presumably, a level of desiccation at which the complex cellular metabolism cannot be maintained. The continued intracellular fluid volume, on the other hand, enables the cardiovascular system to function well. The terminal event is apparently respiratory failure.

Water

Dehydration and its management—Black draws attention to the distinction between dehydration from primary loss of water and dehydration due to reduction of total salt content of the body. It is useful to regard the body fluids as held in three compartments—the plasma, the tissue spaces and the cells, including the erythrocytes. The flow of water from one compartment to another is determined by the amount of protein and salts in the various fluids. Differences in the concentration of individual dissolved substances depend upon the selective permeability of the membranes separating the compartments. Water deficiency of 3-4 days does not produce severe general symptoms, the blood pressure is normal, haematocrit values are not increased and the diodone clearance through the kidneys is not decreased. There is a progressive rise of the osmotic pressure of the body fluids during the period of water deficiency. The bad effects on wellbeing of salt deficiency are greater than is a comparable degree of water deficiency, salt deficiency induced circulatory failure, mental apathy, general exhaustion and haemoconcentration. The urine volume is not so low in salt deficiency as it is in water deficiency. In salt deficiency the whole burden of the fluid loss falls on the extracellular fluid and the effect on the circulatory efficiency is three times as great. Clinically it is important to discover which type is predominant. A small amount of urinary chloride suggests salt deficiency, whereas a large amount of urinary chloride with a low urine volume is a sign that water deficiency predominates. Water deficiency is appropriately treated with administration of water and 5 per cent glucose. Half strength physiological saline and physiological saline are indicated in a mixture of the two types of deficiency. Half-strength physiological saline should be given to children. Salt deficiency should be treated by administration of physiological saline.

Vitamin A

Vitamin A content of human body—Tomaszewski and Działoszynski review the problem of the vitamin A content of human body fluids. It has been shown that in healthy people urine does not contain any trace of vitamin A even after large doses have been taken. In certain pathological conditions, vitamin A may be excreted in great quantities. The question to be answered is whether there is any relation between urinary excretion of vitamin A and its appearance or concentration in body fluids—pleuritic, ascitic, pericarditic, cerebrospinal and amniotic. Most samples examined were of pleuritic origin, since these were most easily available and in most of them vitamin A was present, and was highest in the fluid accompanying neoplastic lung disease. Along with vitamin A, there were traces or small amounts of carotene. No relationship is believed to exist either between the vitamin A content in these fluids and in the urine, or between the vitamin A content and the total protein content of the fluids. Of

25 cases of pleuritic fluid, 21 showed some vitamin A content, and of 13 cases of ascitic fluid, 12 showed vitamin A content. Most of these cases gave negative results in urine. In one case of nephrosis there was a marked increase in vitamin A content of the ascitic fluid and of the urine after a saturation test with vitamin A given by the mouth. Cerebrospinal fluid was examined in 11 cases, and in 2 of these, in which samples were obtained by drainage, vitamin A was found. It therefore seems that drainage plays a part in producing vitamin A in cerebrospinal fluid. Of 6 cases 2 showed vitamin A in amniotic fluid. In physiological fluids, cerebrospinal and amniotic, appearance of vitamin A is exceptional, whereas in pathological fluids its appearance is the rule, although the amount is very small compared with the quantity found in the blood. There is no explanation of the mechanism by which vitamin A passes into the body fluids.

Allen, F. M. B. (1944) *Med. Pr.*, 212, 23.

Black, D. A. K. (1945) *Lancet*, 1, 298.

Elkington, J. R., and Winkler, A. W. (1944) *War Med.*, 6, 241.

Howard, J. E., Parson, W., Stein, K. E., Eisenberg, H., and Reidt, Virginia (1944) *Johns Hopk. Hosp. Bull.*, 75, 156.

Tomaszewski, W., and Dzialoszynski, L. (1945) *Edinb. med. J.*, 52, 74.

Wachstein, M. (1944) *Arch. Path.*, 38, 297.

METABOLISM, BASAL

See also B.E.M.P., Vol. VIII, p. 588; and Cumulative Supplement, Key Nos. 1071–1076.

Basal metabolism in disease

Basal metabolism raised

Creatine content of the urine.—Treusch, Kepler, Power and Haines review the literature relating to creatinuria in hyperthyroidism and the possible relationship between hyperthyroidism and hypertension with increased basal metabolism. They analyse their own results in a series of 35 cases of hypertension and 39 of hyperthyroidism, in which they have attempted to evaluate any connexion between the conditions by estimations of urinary creatine. The total urinary output of creatine in 24 hours was measured by Folin's method while the patients were on ordinary hospital diet. The majority of patients with hyperthyroidism excreted more than 135 milligrams in 24 hours, whereas the majority of patients with essential hypertension, even with an elevated basal metabolism, excreted less than 90 milligrams in the same period. In these cases of essential hypertension spontaneous creatinuria was found to be an unreliable indication of the presence or absence of hyperthyroidism. Three out of 18 hypertensive patients with basal metabolic rates in excess of +15 per cent excreted more than 135 milligrams and 12 excreted less than 90 milligrams. The same variations were noted in 17 hypertensive patients with basal rates less than +15 per cent. There is no direct proportionality between the creatine content of the urine and the basal metabolic rate even in patients with hyperthyroidism. The results substantiate the opinion that the elevation of the basal metabolism in essential hypertension rests on a different physiological basis from that in hyperthyroidism.

Treusch, J. V., Kepler, E. J., Power, Marschelle H., and Haines, S. F. (1944) *Amer. J. med. Sci.*, 208, 310.

MIGRAINE

See also B.E.M.P., Vol. VIII, p. 604.

Aetiology

Allergy

Control of vascular mechanism.—In at least a proportion of cases the basic mechanism of the migraine attack is primary vasospasm which produces the visual disturbances, followed by vasodilatation causing the headache. In other cases it appears that the syndrome is an expression of an exudative diathesis or allergy, i.e. in vascular terms, the primary mechanism is vasodilator in type. Atkinson believes that both theories may be right and that the same dual mechanism of causation may exist as it is said to do in Ménière's syndrome. The groups in Ménière's syndrome can be differentiated by the making of a histamine skin test. Atkinson applied the test to 21 cases of uncomplicated migraine and found that in all of them there was a negative response and that therefore they belonged to the vasospastic group. In 10 out of 22 cases of migraine associated with Ménière's syndrome the histamine test was negative, suggesting that when a primary vasodilator mechanism is at work its effects are more widespread than are those of a primary vasoconstrictor mechanism confined to the region of the calcarine sulcus. Atkinson reports on the results of treatment of the primary vasoconstrictor group with a vasodilator, nicotinic acid. Potassium thiocyanate acts equivalently but is potentially more dangerous. Parenteral administration of nicotinic acid is usually necessary in order to produce results. In one patient who had intravenous injections of 75 milligrams of nicotinic acid within 20 minutes of visual disturbances, the scotoma disappeared in 30 minutes and the patient slept thereafter; the severe headache usually associated with the attack did not develop. Treatment was not, however, invariably successful in other cases.

Treatment

Between attacks

Carbachol as a preventive drug given by the mouth.—James analyses the results of oral

occurred in 1940 among boys living in 8 cottages which were labelled A to H. Each cottage housed 80–90 inmates and 8 employees. Cottages A and F had adolescent boys and young adults, B, C, D and E children of school age who mixed 5 days a week in classrooms and workshops, and G and H housed inmates of low intelligence who were kept apart. The number of inmates susceptible to mumps was unknown. The outbreak was started by an inmate who was admitted to cottage B during the incubation period. Twenty-four hours later he was moved to cottage E, in which mumps was diagnosed 34 hours later. Convalescent serum was not used as there was not enough available for all, or even half the number, of the inmates of cottage E. Thirty-nine inmates and 4 employees in cottages B, C and D contracted mumps, but only one inmate in E. Had prophylactic serum been used the immunity of cottage E would have been attributed to it, but failing this the cause could not be determined. It would seem that there were either fewer susceptible children or that the susceptible children were protected in some undetermined way.

Complications

Rare complications

Presternal oedema.—Gellis and Peters draw attention to the occurrence of presteral oedema in an epidemic of mumps among recruits to the American army from southern rural areas. Presternal oedema in mumps had already been reported by 3 observers since 1918 without any note concerning its frequency. During the epidemic, which involved 502 cases, in 30 (6 per cent) presteral oedema developed, daily observations being made. The epidemic was not of any unusual severity. The oedema appeared on the fifth or sixth day from the onset of glandular swelling and lasted for about 5 days. Twenty-five patients had swelling of one or both parotid glands accompanied by enlargement of one or both submaxillary glands. The other 5 had parotid swelling only. These 5 showed an oedema mild and of short duration. The oedema reached its height on the second day after its onset, having spread downwards to the third interspace and laterally to varying distances up to the mid-clavicular line equally on both sides. In only 3 instances did the skin change to a dull red. Dysphagia was complained of by 2 patients, tenderness to pressure over the sternum by 2 others and hoarseness by 1 other. There was no evidence of involvement of thyroid or thymus gland. In 3 of the cases swelling was marked enough to obscure the supraclavicular and infraclavicular spaces. The aetiology of this condition as a complication of mumps is uncertain. The most probable cause is obstruction to the lymphatic glands since so many patients had concurrent swelling of the submaxillary glands.

Treatment

General treatment

Belladonna therapy in adults.—Potter and Bronstein describe a study of 124 consecutive cases of mumps in adults, at a military hospital in Maryland. Forty-two cases were treated with belladonna. On admission the soldier was given $\frac{1}{160}$ grain of atropine sulphate and then 1 cubic centimetre of tincture of belladonna 2-hourly by the mouth until atropinization was produced, as evidenced by dilatation of the pupils or dryness of the throat or both; the treatment was continued until the patient was cured or until gastro-intestinal discomfort made it necessary to stop administration of the drug. Compared with 82 cases in which belladonna was not given it was found that the drug had no apparent effect upon duration of illness, incidence of complications, duration of orchitis, or on the comfort or the wellbeing of the patient. Analysis of cases showed no difference in the duration of the disease between cases with bilateral and those with unilateral lesions. In studies made during the war of 1914–1918 it was found that most of the cases occurred in soldiers coming from rural communities; in an analysis of incidence in the present series the distinction between town and country dwellers was no longer so clear, probably owing to lessened isolation of community groups. In previous studies on soldiers it has been stated that the majority of cases of mumps occurred within the first 2 months of service, but from the present study the time limit for development of the infection in susceptibles must be increased from 2 months to 1 year. The authors suggest that the long exposure may be consequent upon slightly acquired resistance due to increased urbanization. No significant difference was seen in the duration of the disease in the patients who entered hospital on the first, second or third day of the disease. The complication of orchitis occurred in 11.6 per cent of cases, and only in those of bilateral lesions; a temperature of 103–104° F. was registered when the orchitis appeared.

- Gellis, S. S., and Peters, M. (1944) *Johns Hopk. Hosp. Bull.*, 75, 241.
 Potter, H. W., and Bronstein, L. R. (1944) *Ann. intern. Med.*, 21, 469.
 Siegel, M., and Camp, J. L. (1944) *Amer. J. Dis. Child.*, 68, 163.

given intravenously opens up great possibilities in emergency treatment: using the drip method, 1.5 milligrams could be given in an hour. The drug has often been used for this purpose, as well as in removal of the thymus gland. When large doses are being given, overdosage must be watched for, the most important of the early signs of which are fibrillation or fasciculation of the facial muscles.

Viets² reviews the progress made in the knowledge of myasthenia gravis, and summarizes his experience during the last 8 years with 125 cases, of which 60 were continuously observed at an out-patients' clinic, specially set up at the Massachusetts General Hospital in 1935 in order to facilitate study of the clinical aspects of the disease. Neostigmine (Prostigmin sulphate), first used in 1935, continues to be the main drug employed in treatment; it is also a sensitive diagnostic index. Thus fluoroscopic study of the swallowing reflex reveals that, in a genuine case of myasthenia gravis, normal swallowing is possible after, but not before, the injection of 1 ampoule containing 1.5 milligrams of neostigmine methylsulphate and 0.6 milligram of atropine. With the development of the theory of chemical mediation in the transmission of a nerve impulse across a synapse, it has been established that cholinesterase is inhibited by physostigmine and its derivative neostigmine. Acetylcholine can thus accumulate at the myoneural junction and allow effective transmission of the impulse to the muscles. The average oral intake of 45 ambulatory patients was a total of 163 milligrams of neostigmine bromide, spaced, according to individual needs, over the 24 hours. Neostigmine methylsulphate can be given parenterally in large doses to severely ill patients. Viets suggests that, when the whole acetylcholine cycle is understood, myasthenia gravis may be aetiologically explained, when it may be possible to evolve more specific pharmacological treatment. Ephedrine sulphate, potassium chloride and guanidine hydrochloride are occasionally useful. Of 15 patients subjected to thymectomy, 2 had complete remissions, 5 were improved. Four patients with thymomata did no better than did some patients with a histologically normal thymus gland. Although some relationship apparently exists between the thymus gland and myasthenia gravis there are many difficulties in evaluating the results of thymectomy. The disease may be punctuated by spontaneous remissions, sometimes complete, and moreover thymomata are not necessarily associated with myasthenia gravis. The operative mortality is at present about 25 per cent.

Viets, H. R. (1944)¹ *Amer. J. med. Sci.*, 208, 701.

— (1945)² *J. Amer. med. Ass.*, 127, 1089.

Walsh, F. B. (1945) *Amer. J. Ophthalm.*, 28, 13.

MYXOEDEMA

See also B.E.M.P., Vol. IX, p. 69; and Cumulative Supplement, Key No. 1111.

Morbid anatomy

Cardiovascular system

Oedema of heart and pericardium.—Serous effusions, especially in the pericardium, and a generalized oedema are commonly found in myxoedema, along with noticeable interstitial oedema in the heart muscle. Lange discusses the probable cause of this oedema. Of the factors which cause increased transudative neither increased capillary or venous pressure, nor vasodilatation, nor plethora, nor marked hydraemia are found in myxoedema. While doing circulation time determinations in myxoedematous patients Lange found in them an especially rapid and intense staining of the tissue cells by the dye used. This was remarkable because such patients have a prolonged circulation time. Further investigations were made on 5 patients with myxoedema by means of a dermofluorometer, a photo-electric skin colorimeter, which was used with an injection of fluorescein, a very small molecular dye which penetrates almost immediately from the capillaries into the tissue and diffuses over the entire capillary loop. The abnormally high fluorescence of the skin which was found in these 5 patients could be due only to a high capillary permeability. It could not be due to increased capillary pressure as the number of capillaries per square millimetre is distinctly diminished in myxoedema. Owing to the oedema also, the capillaries are farther from the skin surface and therefore the fluorescence should be decreased, and in direct intracutaneous dye injection experiments no difference in fluorescence was found in the skin of myxoedematous as compared with that of normal patients. Capillary permeability was found to decrease rapidly to the normal after treatment with thyroid extract, coinciding with loss of weight, abundant diuresis and return of the electrocardiogram and cholesterol to the normal. Lange concludes that the high capillary permeability in myxoedema is caused by lack of thyroid hormone. The oedema of cirrhosis of the liver is not accompanied by increased capillary permeability, but the latter does accompany oedema due to under-nutrition and severe avitaminosis.

Lange, K. (1944) *Amer. J. med. Sci.*, 208, 5.

NAILS, DISEASES OF

See also B.E.M.P., Vol. IX, p. 83.

Nail manifestations of diseases other than skin diseases

Nervous diseases

Morvan's syndrome.—Parks and Staples report on 2 cases of the syndrome first described by Morvan in 1893. An 8-year-old boy had been first noticed, when he was 2 years old, to chew his fingers until they bled. Later painless infections developed in the fingers with loss

NEPHRITIS AND NEPHROSIS

See also B.E.M.P., Vol. IX, p. 134; and Cumulative Supplement, Key Nos. 1131–1141.

Classification

Warner's classification

Notes on aetiology and treatment.—Warner describes the principles of causation and the treatment of nephritis. He points out that each nephron of the kidney has a separate blood supply and functions for only short periods at a time. The glomeruli bear the brunt of a bacteriaemia and since only those nephrons in action at the time are attached, focal damage is common. Acute focal nephritis occurs in childhood, due usually to a streptococcal throat infection and there are not usually signs of renal failure. The treatment is to combat the original infection. Acute diffuse nephritis may occur about 20 days after the onset of scarlet fever or of a streptococcal infection of ear or nasopharynx. If it is of toxic origin both kidneys are diffusely involved and signs of renal failure occur. Treatment is rest in bed with restriction of protein and fluids. Subacute nephritis may or may not have a previous history of infection. It can be caused by exogenous poisons or by endogenous poisons as in jaundice, diabetes mellitus, syphilis or pregnancy. Treatment includes the elimination of the cause if known, rest in bed, low or high protein diet depending upon urea clearance and extent of oedema and restricted sodium chloride. Mercurial diuretics are harmful. Chronic diffuse nephritis is the third stage in the development of nephritis. The blood pressure rises progressively and uraemia develops. Chronic focal nephritis is not usually associated with a history of previous infection. It may be due to benign hypertension and kidney destruction is slow. The hypertensive kidney is due to arteriolar spasm which is most noticeable in kidneys, spleen and pancreas and is possibly caused by toxins manufactured in part in the kidneys. The arteriosclerotic kidney is associated with generalized atheroma in old age. The treatment in chronic renal disease is to remove the cause when possible, to eliminate septic foci, to diminish the work of the kidney by diet and to avoid chill and overstrain.

Relation of nephritis to hypertension

Experiments on renal vascular system

Shonyo and Mann, after a review of the literature, present the results of an experimental study of the renal vascular system in several species of animals. After the blood is washed out of the renal blood vessels under controlled pressure, an alkaline synthetic liquid rubber (Neoprene) is injected and is precipitated by strong hydrochloric acid used as corrosive agent. An almost complete cast of the vessels is made which is easy to handle and dissect. In the normal kidney glomeruli occur in three layers, glomerular zone, fascicular zone, which is densely filled, and the reticular zone with large glomeruli. Vessels by-passing the glomeruli do occur in normal kidneys although they are more often seen in pathological kidneys. In several of the authors' instances, two efferent vessels were seen to emerge from a glomerulus. There were indications that direct arteriovenous shunts do occur in normal kidneys although they are most frequently seen in kidneys that have undergone compensatory hypertrophy after unilateral nephrectomy. The glomeruli at the bases of the interlobular arteries are much larger than are those at the terminal portions of these arteries. In hypertensive kidneys—experimentally induced by perinephritis caused by wrapping the kidneys in surgical silk or Cellophane—the afferent arterioles and glomeruli appear to be more pleomorphic than they do in healthy kidneys, since they are usually associated with constricted afferent arterioles. Casts associated with extreme hypertension are quite incomplete, being broken off after passing with difficulty through the larger vessels. In compensatory hypertrophy there is enlargement of the smaller arteries and arterioles and of the glomerular rete, allowing of a greater blood flow through the kidney.

Clinical picture

Glomerulonephritis

Chronic glomerulonephritis and sodium chloride loss.—Thorn, Koepf and Clinton report on 2 cases of salt-losing nephritis simulating acute suprarenal insufficiency. The first patient, a male aged 21 years, gave a history of nocturia and complained of nausea, weakness and vertigo. There were generalized muscular twitchings accompanied by drowsiness and bouts of hiccupping. The state of collapse was characterized by haemoconcentration, dehydration and hypochloreaemia. The breath had a uraemic odour but there was no albuminuria and at no stage of the illness were formed elements found in the urine. Marked improvement occurred with daily intravenous injections of sodium chloride solution and adrenal cortical extract, but therapeutic tests proved that the salt solution was the effective remedy. During the next 2 years the patient was given large doses orally of sodium chloride and sodium bicarbonate. Improvement was maintained apart from episodes of morning vomiting which reacted successfully to intravenous injections of sodium chloride. Tests, however, showed marked reduction in renal function and uraemia recurred when one of the patient's thumbs became infected. Albuminuria, hypertension, increasing nitrogen retention and moderate oedema preceded the terminal coma. Necropsy disclosed cystic fibrotic kidneys with great distortion of architecture. The glomeruli were decreased in number and many tubules were extremely dilated. The suprarenal glands were normal. The second patient was a young woman whose illness pursued an essentially similar course. Post-mortem examination of the kidneys revealed a picture corresponding to diffuse glomerulonephritis in the final state. The suprarenal glands

showed no change of any significance. The authors consider that renal disease rather than suprarenal insufficiency was associated with the excessive loss of sodium, chloride and water. Less severe loss of sodium and chloride may occur in chronic nephritis and it is suggested that in these circumstances small quantities of sodium chloride and sodium bicarbonate may benefit this disease.

Shonyo, E S and Mann F C (1944) *Arch Path*, 38, 287

Thorn G W, Koepf, G F, and Clinton, M, Jun (1944) *New Engl J Med*, 231, 76

Warner, E C (1944) *Med Pr*, 212, 86

NERVE INJURY AND REPAIR

See also B E M P, Vol IX, p 160, and Cumulative Supplement, Key Nos. 1142-1144

Morphological changes resulting from nerve injury

Microscopical changes

Changes at nerve endings—Dublin reports on observations on nerve-muscle specimens taken from adult unselected rabbits and prepared by Ranvier's method of gold chloride impregnation. Comparisons were made between specimens from control animals and those from animals subjected respectively to curarization, hypothermia and strenuous exercise. The observation that the structure of the untreated nerve endings varied considerably suggested that comparisons with pathological conditions should be made on a broad average or general tendency basis and suggested also a comparison with the variation in the renal glomeruli when functioning and when at rest. Although Lindsley held that the contracting unit of muscle is approximately 1 millimetre in diameter, variations in structure in motor endings were observed in single microscopical fields in Dublin's experiments. After curarization by subcutaneous injection of Intocostin, no remarkable degree of variation from the normal in structure of motor nerve endings was observed but slight contractions of endings occurred. Specimens taken from rabbits which were packed in ice after light sedation with subcutaneous doses of barbiturate, showed no appreciable degree of variation from the normal although here again there was slight contraction of endings. At the height of vigorous exercise rabbits were stunned and specimens were rapidly removed. In these there was observed extensile expansion of nerve endings simulating that described by Carey.

Experiments with nerve constriction—Denny Brown and Brenner describe experiments to show the lesion which results in a peripheral nerve from pressure by a spring clip, the pressure imitating the way in which a constricting band of scar tissue disturbs neural function. The clips were applied to the exposed sciatic nerves of anaesthetized cats. Compression for 2 hours with a tension of 170-430 grammes caused paralysis which lasted 5-18 days. Sensation was little affected and the distal portion of the nerve fibres did not degenerate. The compressed area showed gaps in the myelin sheath at the nodes of Ranvier, defects in the staining properties of the axis cylinder, oedema, and scavenger cells. Motor function recovered early, but restitution of the myelin defect was only slight after 6-8 weeks and was still defective after 6 months. Continuous compression with a tension of 5-7 grammes caused narrowing of the compressed segment and oedema of the nerve on each side of the constricted region. Swelling of the myelin in the oedematous region caused striking histological changes in myelin and in axis cylinder and there was mobilization of the large pale endothelial cells. There was not any interference with conduction. With a continuous compression of 44 grammes there was preservation and necrosis of myelin and of axis cylinder under the clip and oedema and degeneration above and below the compressed area. The proximal degeneration was of the type which is due to excessive ischaemia. Continuous compression with a tension of 9 or 10 grammes caused onset of motor paralysis between the fifth and the eighth day. This lasted for up to 25 days and recovery was rapid. There was segmented loss of myelin as well as oedematous changes. Restitution of myelin occurred gradually 6 weeks after the beginning of the experiment. There was impaired argentophilic property of the demyelinated axis cylinder. The characteristic histological lesion and dissociated paralysis which are caused by pressure on a nerve are due to ischaemia and form a distinctive type of neuropathological reaction. The dissociation between sensory and motor function is due to a functional property of the disorder of the axis cylinder and not to a selective effect related to the size of the fibre.

Symptoms of nerve injury

Paralytic

Traumatic ischaemia of peripheral nerves—Parkes discusses traumatic ischaemia of peripheral nerves as illustrated by 15 cases of injury to a limb complicated by multiple nerve lesions, observed at the Scottish Peripheral Nerve Injuries Centre. In most cases there was a history of injury several months before the patient first came to the Centre with development soon after the injury of gross swelling of the limb or of other signs of severe circulatory disturbance. Paralysis of varying extent of the deep nerve trunks of the affected part occurred, with sensory loss, the anaesthesia being often of the stocking or the glove type, commencing in the digits and spreading centripetally. During the early stages and during recovery, some dissociation between various forms of sensation was occasionally found and delayed response to pinprick was noticeable in most cases. Motor loss was usually confined to the intrinsic

muscles of the hand or foot but might affect some of the more proximal muscles. Mild muscle contracture was often present in the later stages, although it was seldom of the true Volkmann type. Spontaneous recovery, if delayed for more than the first few weeks after injury, occurs very slowly and is dependent upon nerve regeneration. The most satisfactory explanation of the nerve lesions is ischaemia of the nerve trunks due to traumatic arterial spasm, or to pressure beneath the deep fascia caused by extravasation of blood and tissue fluids, or to both. The pressure theory is borne out by experiments made in 1931 on the intact human subject, in which similar sensation phenomena and paralyses were caused by the pressure of a special clamp on the nerve trunks of the arm and, most convincingly, by 2 cases of slight trauma occurring in haemophiliacs, in which large haematomata caused similar nerve lesions. Early recognition of the condition and appropriate surgical and other treatment for relief of the ischaemia should prevent the occurrence of nerve degeneration.

Treatment of nerve injury

Methods of repair

Different types of nerve graft.—Davis, Perret, Hiller and Carroll describe the functional results of repair by (1) end-to-end suture, (2) autogenous grafts and (3) homogenous grafts, of experimental sections and gunshot wounds inflicted on the sciatic nerve of cats under Nembutal (soluble pentobarbitone) anaesthesia. Microscopical and clinical investigations were then made. Well developed axis cylinder and myelin sheath formation were noted in the distal segments of the nerves 45 days after end-to-end suture, in presence of large amounts of myelin decomposition products. Regenerating nerve fibres appeared during the first week after suture. There was always satisfactory nerve regeneration in the distal nerve segment. In all methods of repair, swelling is present at the suture lines, the result of the endoneural and perineural mesodermal proliferation which unites the severed nerve ends, or the graft, to the proximal and distal nerve segments. Muscular atrophy recovers more quickly after end-to-end suture than after nerve grafting. Motor function, as measured by response to direct electrical stimulation of the repaired nerve, reappears earlier and remains better after end-to-end suture; the first signs of recovery after severance of the sciatic nerve in the thigh are plantar flexion of first the foot and then the toes, and dorsiflexion of the foot. Dorsiflexion and fanning of the toes are late signs of recovery; normal gait and stance reappear even later. Contractures, which occur during the process of denervation, and most commonly involve foot dorsiflexors and toe plantar flexors, more often follow homogenous grafts than they do autogenous grafts or end-to-end sutures. Trophic disturbances, including ulcers, were observed in all the paralysed limbs and healed very slowly. In gunshot wounds, with or without interruption of nerve continuity, microscopical study revealed confusion effects within the nerves and extensive traumatic damage was found in proximal and distal nerve segments over a long distance from the site of trauma.

Importance of muscle and sensory tests

In a paper on peripheral nerve injuries in battle casualties Russell and Harrington stress the importance of early diagnosis and correct treatment, delay in diagnosis and incorrect treatment gravely affecting the subsequent usefulness of the attacked limb. Of 132 cases of upper limb nerve injuries which were admitted to a nerve injury centre in the Middle East 61 patients showed some degree of contracture or stiffness of the finger joints, in most cases due to the nerve and not to the associated forearm muscle injury. The voluntary action of the muscles is tested by getting the patient, if he is well enough, to carry out specific movements against resistance or to maintain posture against resistance. If sensory tests, which are less reliable and take longer, are used the hand or foot is the essential part of the examination in most cases. The presence of anidrosis of the anaesthetic skin area is a useful objective sign, and reflex changes are also useful confirmatory evidence in some cases. In the testing of injuries of the principal nerves in the upper and lower limbs it should be remembered that nerve injury cannot cause apparent drop-wrist in wounds of the distal half of the forearm. It is noted that injuries to the posterior tibial nerve or to its terminal cutaneous branches cause anaesthesia, analgesia and anidrosis of the sole of the foot without paralysis of the long flexors of the toes. Failure to recognize analgesia of the sole of the foot is a serious although a common error. In early treatment excessive splinting is very harmful because it causes stiffness of the joints of the hand. In order to prevent "frozen" hand early active or passive movements should be advised and the patient be encouraged to maintain the range of movement of the joints. Drop-foot, unlike drop-wrist, should be supported as soon as possible.

Davis, L., Perret, G., Hiller, F., and Carroll, W. (1945) *Surg. Gynec. Obstet.*, 80, 35.

Denny-Brown, D., and Brenner, C. (1944) *Arch. Neurol. Psychiat.*, Chicago, 52, 1.

Dublin, W. B. (1944) *J. nerv. ment. Dis.*, 100, 275.

Parkes, A. R. (1945) *Brit. J. Surg.*, 32, 403.

Russell, W. R., and Harrington, A. B. (1944) *Brit. med. J.*, 2, 4.

NEURALGIA, GLOSSOPHARYNGEAL AND TRIGEMINAL

See also B.E.M.P., Vol. IX, p. 174; and Cumulative Supplement, Key Nos. 1145 and 1146.

Trigeminal neuralgia

Aetiology and pathology

Sphenopalatine ganglion lesions.—Dysart discusses modern views regarding neuralgia caused

from the general practitioner's viewpoint. The syndrome is characterized by motor disturbances, loss of tendon jerks with preservation of cutaneous reflexes, paraesthesias with slight disturbance of objective sensibility, tenderness on pressure of the muscles, little change in the electrical reactions of the nerves or muscles and noteworthy hyperalbuminosis of the cerebrospinal fluid in the absence of cytologic reaction, called albuminocytological dissociation. Guillain has stressed the albuminocytological dissociation of the cerebrospinal fluid and the favourable prognosis. The former establishes the differential diagnosis from the initial stage of poliomyelitis, but repeated lumbar punctures may be necessary because the fluid may have a normal protein content in the early stages of Guillain-Barré syndrome; the aetiology of the syndrome is unknown, but it is generally considered to be due to a virus infection, and the patient is afebrile. The author describes in detail a case which occurred at the height of an epidemic of mononucleosis, but frequent blood slide examinations and a Paul-Bunnell precipitation test failed to reveal any connexion between the epidemic and the case of radiculoneuritis described. No specific treatment is known but Guillain suggests that antiseptic agents are useful and recommends daily intravenous injection of 1–2 grammes of sodium salicylate in serum containing 10 per cent glucose, or intravenous or intramuscular injections of quinine, methenamine (hexamine) or colloidal silver. These antiseptic remedies could be combined with ionization or iodine or calcium administered by the transcerebromedullary path, with warm baths and irradiation. On these suggestions the author comments that the general practitioner "will no doubt obtain equally good results with slightly less science".

Local or interstitial neuritis

Clinical picture

Bilateral acoustic neuritis.—Johnson describes a case of bilateral acoustic neuritis, and reviews the literature. Various causes of the disease have been given: focal infections from tonsillitis or a dental abscess, diphtheria, meningitis or other acute infective diseases, syphilis, vitamin deficiency, and the toxic effects of quinine, arsenic, the salicylates and possibly the sulphonamides. Acoustic neuritis is described as of sudden onset, with tinnitus and deafness, vertigo, disturbances of equilibrium, spontaneous nystagmus and vomiting. Both the cochlear and the vestibular branches of the auditory nerve may be involved or only one or other of them. The loss of hearing varies greatly. A case of auditory nerve neuritis resulting from focal infection in the appendix has been described as well as an unusual complication of osteomyelitis—complete nerve deafness. Severe bilateral tinnitus and impairment of hearing has occurred after extensive radiation treatment of carcinoma of the cervix. The case described was that of a man aged 23 years, who was admitted to hospital with acute follicular tonsillitis. While in hospital he complained of pain and deafness in the right ear. After recovery from tonsillitis and temporary absence from hospital he was readmitted complaining of complete deafness in the right ear, a roaring sensation in the left, and pressure over both eyes. Both tympana were intact without any evidence of inflammation. Sinuses were normal and no focus of infection was found anywhere after complete investigation of all systems. Various treatments were tried but the deafness progressed and became complete in both ears 6 months after its onset. No clear cause could be found, and the auditory nerve alone appeared to be involved.

Briskier, A. A. (1944) *J. nerv. ment. Dis.*, **100**, 462.

Johnson, M. R. (1944) *Arch. Otolaryng.*, Chicago, **40**, 261.

Kennedy, R. T. (1944) *Med. J. Aust.*, **2**, 231.

Lewey, F. H. (1945) *J. Pediat.*, **26**, 165.

NEUROSYPHILIS

See also B.E.M.P., Vol. IX; p. 224; and Cumulative Supplement, Key Nos. 1151–1166.

Intracranial syphilis

General paralysis of the insane

Cerebrospinal fluid and prognosis.—Lange and Harris discuss the value of qualitative and quantitative examination of the cerebrospinal fluid in the diagnosis and prognosis of general paralysis of the insane, with special stress on the necessity of quantitative differentiation. The formula of the disease is very distinctive, and qualitatively is characterized by the combination of positive reaction for syphilis and a dementia paralytica (parenchymatous) colloidal gold curve, and quantitatively by stronger reactions than any found in other forms of neurosyphilis. False dementia paralytica curves, due either to confusion with first zone curves or to an unsatisfactory pH of the milieu, must be eliminated. In the true curve the presence of an abnormal pseudoglobulin-like dementia paralytica substance is shown, indicating extensive parenchymatous degeneration. This explains its grave prognostic significance. Striking quantitative differences in dementia paralytica formulae are shown when quantitatively standardized methods are used, particularly in the determination of total protein and in the colloidal gold test. Only about one-third of the cerebrospinal fluids which were submitted for control of treatment gave true dementia paralytica formulae, two-thirds being notably weaker. It cannot be determined whether or not a true formula detected in the early asymptomatic stage means prospective development of the disease but, in any case, the question of the presumptive resistance to antisypilitic treatment is of much greater importance, since it determines the selection of adequately intensive therapy. The results of quantitative methods suggest that the resistance to antisypilitic treatment roughly parallels the strength of the dementia paralytica

states that experiments over a period of 8 years show these objections to be ill founded. He has treated with large fluid intakes myocardial and valvular diseases, eclampsia and pre-eclamptic toxæmias and advanced nephritis with the nephrosis syndrome. The patients have tolerated the regimen well and have experienced greater comfort than they have when they were on restricted fluids. The general scheme of treatment was to give large amounts of water orally or by vein and a neutral diet in order to regulate the ingestion of sodium. Such treatment ensured reduced amounts of salt and sodium and a slight excess of acid-ash. In severe congestive heart failure the handicapped kidneys appear to be capable of regulating the concentration and electrolyte patterns of the extracellular fluid while permitting great losses of excess interstitial fluid, in spite of the daily ingestion of volumes of water and the daily loss of large amounts of urine water which actually exceed the blood volume and approach the normal volume of the interstitial fluid. Schemm quotes the observation of Sir Thomas Witherley made in 1690: "That Water should expell Water is a Miracle beyond any of St. Winifred's".

Schemm, F. R. (1944) *Ann. intern. Med.*, 21, 937.

OEDEMA, HEREDITARY

See also B.E.M.P., Vol. IX, p. 282.

Clinical picture

Two cases of Milroy's disease

Two cases of congenital hereditary lymphoedema (Milroy's disease) occurring in siblings are reported on by Glaser, who also briefly reviews the relevant literature of this rare disease. His first patient, a first-born male, was seen when aged 7 months because of oedema of feet and legs which was more marked in the right limb and had been present since birth. He had an oedematous foreskin, which did not bleed during subsequent circumcision, its cut surface appearing tough, white and translucent. Microscopically, it contained dense collagen fibres and thick-walled structures of capillary size, which were apparently lymphatic vessels since the walls contained no muscle. These definite tissue changes rule out the mere stasis of the lymphatic fluid or blood but support the most accepted aetiological theory of congenital malformation of lymph vessels. A wheal absorption test was 40 minutes for arms and 30 minutes for legs. The boy's younger sister, seen when aged 17 months, had a swelling of the right foot and leg which had been present since birth. In both children the laboratory reports were all within normal limits, substantiating the fact that this is not a constitutional disorder. Skiagrams in each case showed physiological bones and joints of the lower extremities, as well as a small spina bifida of the second sacral segment, which was not considered to be significant. In the boy's case little or no improvement resulted from elevation of the legs and application of elastic bandages to the oedematous extremities, or of the wearing of Unna's boots after preparatory elevation and snug application of elastic bandages for 24 hours. Temporary slight improvement in the girl's condition ensued from similar treatment.

Glaser, K. (1944) *J. Pediat.*, 25, 337.

OESOPHAGUS DISEASES

See also B.E.M.P., Vol. IX, p. 287; and Cumulative Supplement, Key Nos. 1176-1188.

Tumours

Non-malignant

Differential diagnosis of benign oesophageal conditions.—Harper and Tiscenco report on a case of intrinsic extramucosal benign tumour of the oesophagus, verified, after successful removal, as a leiomyoma. Its morphological features as observed in radioscopy and in spot films are analysed. During the passage of barium, a smoothly outlined fork-like appearance, resulting from splitting of the barium column where it impinged on the tumour protruding into the lumen, was observed at the level of a fusiform dilatation. In tangential projection the upper margins of the defects were sharp, without definite undermining. In lateral projection, an apparent filling defect, due to a slit-like deformity of the lumen, was seen. A smooth variable "mould" effect resulted from contact of the barium with the foldless mucosa stretched over the submucous tumour. Radioscopic detection and radiographic visualization of a smoothly outlined soft tissue mass was obtained and its mobility perceived during deglutition and on forcible respiration. In tangential projection, an imaginary line restoring the continuity of the mucosal outline intersected the mass in its longest vertical measurement, which the authors consider particularly significant as an indication of its intramural origin. The fundamental problems of diagnosis between oesophageal mucosal, submucosal and attached extrinsic tumours are discussed. The relation of the circumference of the soft tissue mass to the affected oesophageal segment is an important sign in distinguishing between intrinsic extramucosal tumours and attached extrinsic processes. In studying any deformity of oesophageal outline, the main features differentiating a benign extramucosal tumour from a carcinomatous deformity would be: (1) a bulky mobile soft tissue mass attached to the deformed area; (2) preservation of the normal mucosal folds in its immediate vicinity; (3) variation of the shape and dimension of the filling defect; (4) absence of actual obstruction and of mucosal erosion. Confirmation of the radiological diagnosis of an intrinsic extramucosal oesophageal tumour by oesophagoscopy and, if possible, by biopsy is always desirable.

Malignant

Treatment of oesophageal carcinoma with radium—Lederman and Clarkson describe radium treatment of cancer of the oesophagus. Although these growths are radiosensitive, treatment is usually, owing to the insidious nature of the condition, late and is made difficult by the relative inaccessibility and the relation to important viscera of the oesophagus. The procedure adopted depends upon whether cure or palliation is attempted. The authors classify these growths as pharyngo-oesophageal, mid-oesophageal and cardio-oesophageal. The first group, if the growths do not extend below the first dorsal vertebra, are treated according to tele-radium technique in which dosage falls progressively from skin via lymphatic gland areas to the primary site. Mid-oesophageal tumours are treated by radium bougie or radon implantation. The authors emphasize the importance of meticulous technique in bougie treatment and describe details of the method adopted at the Royal Cancer Hospital, London. Of the various methods of radon seed insertion the authors prefer Negus's technique in which the seeds are linked in tandem either by catgut or by being loaded in silk or rubber tubes. The treatment—which in any case is only palliative—of cardio-oesophageal tumour involves laparotomy and insertion of the seeds into the tumour substance through the serous surface, avoiding penetration into the lumen of the stomach. The risks of peritonitis are small.

Harper, R. A. K., and Tiscenko, E. (1945) *Brit J Radiol*, 18, 99.

Lederman, M., and Clarkson, J. (1945) *Brit J Radiol*, 18, 22.

OVARY DISEASES

See also B E M P, Vol IX, p 318, and Cumulative Supplement, Key Nos 1191-1196

Tumours**Aetiology and classification**

Report on fifty tumours—Novak presents the report of the first 50 cases on the records of the Ovarian Tumour Registry which is conducted by the American Gynaecological Society. The work of the Registry is carried on by 5 doctors, all of whom study the material submitted. In the majority of the cases reported on, which included a wide variety of interesting tumours, the diagnosis was essentially unanimous. Nine granulosa-cell carcinomata, 4 secondary adenocarcinomata, 4 thecomata, 4 serous papillary cystadenocarcinomata, 4 Brenner tumours, 3 Krukenberg tumours, 3 dysgerminomata, 2 suprarenal tumours and 2 fibromata are tabulated. Primary adenocarcinoma, arrhenoblastoma, mesonephroma, lymphosarcoma, serous cystadenoma, pseudomucinous cystadenoma, endometrial cyst and corpus luteum cyst each occurred once. In 7 cases the diagnosis was doubtful. One colloidal tumour was variously classified as mesonephroma, atypical serous cystadenoma and endothelioma malignum. Another was considered to be an atypical Brenner tumour or a fibro adenoma with metaplastic changes. A rapidly growing tumour was variously classified as lymphosarcoma, atypical dysgerminoma, highly undifferentiated sarcoma like arrhenoblastoma, round-cell sarcoma and lymphoid hyperplasia. The diagnosis in one metastasizing tumour lay between dysgerminoma, medullary or metastatic cancer of unknown origin and mesothelioma peritonei malignum, and in another between malignant thecoma, sarcoma, fibroma, malignant dysgerminoma and glioma of teratomatous origin. One was considered to be either a metastatic Ewing's tumour or a granulosa cell tumour and another, arrhenoblastoma, metastatic adenocarcinoma or granulosa cell tumour. Novak emphasizes that it is not only rare tumours or those causing difficulties in diagnosis which are wanted for the Registry, since even in such common types as serous papillary cysts there is doubt about the prognosis and histological significance, malignant or non malignant. The best possible clinical date and material for study—slides, blocks of tissue or entire specimens—are desired. It is hoped that the preliminary report will bring home to clinicians and pathologists the importance of contributing to a cooperative project of this kind, the object of which is to correlate authoritative pathological study with the corresponding clinical course. Anticipated benefits include acquisition of knowledge concerning histogenesis, prognosis and group characteristics so that a more satisfactory nomenclature may eventually be worked out.

Meigs's syndrome—Gardiner and Lloyd-Hart review 38 cases in the literature and give details of one case which came under their own observation, of Meigs's syndrome—ovarian fibroma with ascites and hydrothorax. The point is emphasized that the innocent nature of the condition is apt to be overlooked and no operative treatment undertaken. On the other hand, operative treatment may be too radical, as happened in the authors' own case. The condition is not well recognized in Great Britain. In addition to shortness of breath, pain in the chest and abdominal enlargement, the authors' patient had effusion into the right knee joint. In the majority of cases the hydrothorax is on the right side, the tumour is large and feels hard and there is evidence of abdominal effusion. The symptoms and signs justify an exploratory operation. The occurrence of ascites with ovarian fibroma is common. It is difficult to explain the condition of hydrothorax. The authors believe that pressure by the hard tumour on the lower part of the inferior vena cava increases the load on the azygos system, dilating these veins and causing transudation into the right pleural cavity. Variations in the structure of these veins may account for the effusion being sometimes on the left side, sometimes on both sides. In the authors' case the removal of the tumour cleared away the effusion in the patient's right knee joint. Gardiner and Lloyd-Hart assume that the effusion case was this effusion noted. Simple removal of the fibroma completely cures the syndrome.

Clay, Johnston and Samson describe 2 cases of Meigs's syndrome (hydrothorax and ascites in association with fibroma of the ovary) which occurred in Aberdeen within one year. In each case there was a history of dyspnoea, loss of weight, fatigue, cough and pain in the chest; both cases showed a large right pleural effusion, a small quantity, less than a pint, of fluid in the peritoneal cavity and a large ovarian fibroma, right-sided in one case, left-sided in the other. Neither tumour showed signs of malignancy and evidence of tubercle was not found in chest or abdomen. After removal of fluid and tumours both patients made good recoveries. No satisfactory explanation can be given of the phenomenon; the suggestions that it may be due to lack of drainage of the right chest by the azygos vein, repeated minor trauma to the peritoneum by the fibroma or congenital communication between the abdomen and chest have none of them been satisfactorily substantiated. This is a rare condition, only 28 cases having been recorded in the literature, 27 in the United States of America and one in England, but 2 cases occurring in one year among a relatively small population suggest that some—unfortunately, since operation effects a cure—may go unrecognized, simulating as they do advanced carcinoma of the ovary or severe cardiac, renal, pulmonary or hepatic disease in which operation would not be undertaken. The syndrome should always be considered in a differential diagnosis of abdominal and chest effusions.

Clinical types

With special reference to Meigs's syndrome.—Rubin, Novak and Squire report on 78 cases of ovarian fibromata and theca-cell tumours, with special reference to production of ascites and hydrothorax (Meigs's syndrome). In the first 23 cases, no distinction having been made then between the two types of tumour, ascites occurred 9 times, bilateral hydrothorax once. Ascites occurred only twice among 30 cases of ovarian fibroma, but 7 times among 23 cases of theca-cell tumour one of which was also associated with a right-sided hydrothorax. The authors' material is tabulated, in cases of ascites, as regards size of tumour, amount of fluid and condition of the tumour, especially whether cystic and oedematous, or haemorrhagic. The ascitic fluid possibly originates from the tumour itself. In this connexion Geibel's observation on the oozing of fluid from an ovarian fibroma placed in a dry vessel should be verified. Careful study of the condition of the tumour's surface and of its lymphatic and blood vessels, including those of the pedicle, may show factors causing lymph stasis or congestion which would possibly allow of exudation of tissue fluid on the surface. The anatomical routes by which fluid may reach the pleural from the peritoneal space may be blocked by living cells, cell debris or chronic inflammatory serosal changes. The prevalence of right-sided hydrothorax is attributable to the better development of diaphragmatic lymphatics and the stronger pumping action of the higher diaphragm on the right side. In each case of Meigs's syndrome the physical characteristics, including osmotic pressure, of the ascitic and pleural effusions should be determined. Hydrothorax will more likely occur when the ascitic fluid is poor in colloids and when the rate of pleural absorption and deportation of fluid allows of its accumulation.

Granulosa-cell and theca-cell tumours.—Ingraham, Black and Rutledge present detailed reports on 2 cases of granulosa-cell and one of theca-cell tumour occurring in women, all well past menopausal age. In each the ovarian tumour was associated with an enlarged uterus showing excessive and abnormal endometrial hyperplasia. The histological appearances in each case showed stromal and myometrial invasion by endometrial glands lined by epithelium of atypical appearance, the whole picture being sufficiently hyperplastic and atypical to be classed as adenocarcinoma. In one case the endocervix also was hyperplastic. The definition of cancer of the body of the uterus is considered to be equivocal. Thus, the criteria of continuous and irreversible proliferation, with invasion and eventual perforation of the myometrium with peritoneal extension, and establishment of metastases by way of the lymphatic vessels or the blood, are not all present in many true carcinomata, nor have they been reported on in cases of excessive endometrial hyperplasia coincident with granulosa-cell or theca-cell tumours. There is no histological criterion which allows distinction between tumour-induced endometrial proliferation and true carcinoma of the body of the uterus. The whole question of the relationship of the ovary to uterine body cancer remains unanswered. The authors cite Stohr's case in which spontaneous regression of endometrial hyperplasia—considered to be adenocarcinoma—occurred after removal of a granulosa-cell tumour and a normal menstrual cycle returned under the influence of the remaining ovary. The problem remains whether or not true endometrial carcinoma would regress if all abnormal sources of oestrogenic substances, such as follicular cysts and granulosa-cell and theca-cell tumours, were removed. It has been suggested that extra-ovarian sources of abnormal oestrogenic substances, and possibly also of chemically related carcinogenic substances, may originate during metabolism of cholesterol and bile salts. Other reports indicate that normally functioning ovaries do not prevent the development of endometrial carcinoma, and that hyper-oestrinism or the unopposed action of oestrin is not responsible for such development. Further search for aetiological factors within the ovary may still be indicated because of the frequency (10 per cent incidence in 42 cases reported on) with which endometrial carcinoma and granulosa-cell and theca-cell tumours are associated. Moreover, the apparent infrequency of endometrial carcinoma in surgical castrates is noteworthy.

Benign theca-cell tumours of ovary.—McGoldrick and Lapp give details and discuss 4

examples of benign theca cell ovarian tumours of which, since Loeffler and Priesel reported 6 cases in 1932, about 82 have been described in the world literature. Some authorities maintain that theca-cell and granulosa cell tumours have a common origin and are derived from embryonic mesenchyma, others consider that they develop from unused and immature theca cells of the ovarian parenchyma, thus differing from granulosa cell tumours. Sixty five per cent of theca cell ovarian tumours are postmenopausal, the remainder occur between puberty and the climacteric. The symptoms in the latter group may be menorrhagia, often preceded or succeeded by hypomenorrhoea or amenorrhoea, but menstrual disturbances may be absent. Of the 4 examples described by the authors one very large tumour, in a girl aged 17 years, caused no menstrual irregularity. In the postmenopausal patients atypical bleeding, cyclic or irregular, scanty or profuse, occurs and there may be rejuvenation of atrophied breast tissue, recrudescence of libido and revitalization of vaginal mucosa. The curve of age incidence relating to 75 patients ascended from 3 cases in a 15-19 years age group to a peak of 28 cases in a 50-59 years group, descending again to one case in a 90-95 years group. Theca cell tumours have occurred in association with other ovarian tumours, especially cysts, and with uterine fibroids, but Geist and Games did not find any relation between theca cell and other growths. Hitherto the presence of only 3 malignant theca cell tumours has been reported.

Clinical picture of all types

Investigation of cystic fluids—Watts and Adair describe the chemistry of ovarian cyst fluids. Since often only certain cyst cavities in some multilocular malignant tumours show malignancy, they considered that a study of fluids from different cavities might show some chemical differences in the metabolism of malignant and benign cells, and that since the physical and chemical constituents of the fluids vary in different cysts, such examinations might be of use in the classification of the tumours. Thirty two fluids were examined—16 from benign cysts, 12 from malignant cysts and 3 from parovarian cysts. A histological study of the cyst wall was made at the same time. The fluid was aspirated from the cyst as early as possible in order to prevent diffusion of the chemical constituents owing to changes in the cyst wall. Great variation was found in the specific gravity (from 1.005 to 1.051) and in the total solid values. As compared with serum, the glucose values were low, and in this respect the fluids differed from transudates. Certain workers examining the synovial fluid, have found the latter to have a low glucose value, this being coincident with an infected synovial fluid. When sterile synovial fluids were investigated low glucose values were found when there was a high leucocyte count, such low values were experimentally proved to be glucolysis. Since no evidence of inflammation was found in the authors' series of fluids the possibility of the glycolytic effect of tumour tissue had to be considered. There was great variation in the concentration of electrolytes. High chloride values were found to be associated with low protein values. The authors emphasize that great variation in the chemical composition has been found not only in fluids from different types of cysts but also in fluids from the same types and in fluids from different loculi of the same cyst. When correlated with the histology of the cyst wall high protein and potassium values with low chloride value are found when the cells of the wall show much secretory activity. If they show less activity the fluids are found to be low in potassium, total solids and protein and to be high in chloride.

Treatment

Radiotherapy in malignant disease of the ovary—In a Discussion on the radiotherapy of malignant disease of the ovary, Brews stated that the remote prognosis of surgical treatment alone was very poor, that both surgery and radiotherapy were handicapped by the insidious progress of the disease and that, in general, surgery should be subordinated to radiotherapy. He stressed the need for the radiotherapist to be present at laparotomy or to be given a complete report of the character and extent of the disease. Tod stated that small doses of x rays after incomplete removal were not effective prophylactically and that only full courses were of use. Complete treatment meant using large fields covering most of the abdomen in a planned course and was based on the principle that incomplete surgical removal left the whole of the peritoneal cavity potentially involved. Multiple fields and a device known as the trunk bridge were used. The dose was 3,000 r in 3-4 weeks. This involved the delivering of an integral dose of 40-50 megagram roentgens. Tolerance was estimated by leucocyte counts, the standard of safety usually being over 3,000 total leucocytes per cubic millimetre. She made use of Goodfellow's observation that a lymphocyte fall always preceded the fall in polymorphonuclear cells. Systematic use of this method of radiotherapy would appreciably improve the survival rate in malignant disease of the ovary. Ellis suggested statistical co-operation between hospitals in order to give sufficiently large groups so that unequivocal conclusions could be drawn. The implication was strong that in cases treated with x rays only the patients survived longer than did those in cases treated with x rays plus radium plus statistician's viewpoint, definite conclusions on the value of radiotherapy were scanty. Green expressed doubt concerning the wisdom of giving such large dosage as had been advocated, which he thought must prejudice the health of the patient.

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PAIN

See also B.E.M.P., Vol. IX, p. 359.

Physiology

Clinical characters of pain

Ganado is of the opinion that pain consists of a group of distinct feelings, each of which has clinical characters of its own. Somatic pain may arise from the surface or the subsurface or from the deep tissues. It is possible to demonstrate the variations in the type of somatic pain by injecting hypertonic saline solution into the tissues. Tests for deep pain are rendered more precise by the injection of a local anaesthetic into the superficial structures. All the characters of surface pain tend to promote accuracy. The pain is very well located and is never referred to a distance. The power of discrimination is good. Pricking and burning are the only sensations of pain from the normal skin and from sensitive mucosae. Itching is a sensation occurring in skin rendered hyperalgesic by injury. Pain arising from the deep tissues has an aching quality and is different from subsurface pain. Deep pain is persistent, very diffuse and non-discriminative. It radiates to a distance. The extent of this radiation is proportional to the depth of the injured tissue. The distribution of deep pain follows a segmental pattern, a phenomenon which is equally characteristic of pain arising from the hollow viscera. Many internal organs are insensitive, but pain may arise from viscera embryologically connected with the somatic tissues. The reflexes and reactions which accompany deep pain tend to inhibit activity, whereas cutaneous pain may be associated with an invigorating reaction. It is concluded that a complex mechanism presides over the manifestations of deep pain in each segment. The mechanism can be set in motion even by limited injury, with the result that the pain lacks discrimination and is widely distributed. The connexions of the superficial tissues are more restricted, and those associated with the skin are quite distinct.

Anatomical basis

The spinal pathway

Lesions of the intervertebral disc.—The part played by lesions of the intervertebral discs in the causation of low back pain is discussed by Mooney. Central nuclear protrusions, which usually appear from the age of 17 years onwards, cause lumbar or thoracic pain. Treatment is by immobilization, which is usually a complete success since the pain stops when a bony barrier is formed. Epiphysitis occurs between 14 and 17 years, pain results and wedging may be a prominent feature with consequent disability. Immobilization is necessary and healing usually takes 6 months. After growth has ceased a case may show wedging, nuclear escape and obvious disc damage. A tuberculous lesion must always be eliminated. In the tuberculous lesion the disease process starts in the centrum and eventually damages the disc, thus working the opposite way to that of nuclear lesions. Disc rupture may occur after trauma in young adult life. The initial symptoms are low back pain followed later by radicular pain, often severe. This radicular pain is caused to a great extent by oedema of the dural sheath. Both surgical and conservative treatments are employed. In one type, an annular tear with an intact or nearly intact posterior nucleus, the pressure can be relieved by surgical incision. With increasing years discs may gradually lose vitality. A common manifestation of loss of disc vitality may be the formation of osteophytic spurs around the vertebral margins, which in itself is not a cause of pain. When assessing the possibility of osteoarthritis of the spine, the spur formation must not be considered as a cause of pain, and further evidence, such as actual disc destruction or interarticular joint changes, must be sought. Finally Mooney discusses the posterior nodal protrusion, a particularly localized lesion, in which nuclear tissue is forced backwards through a destroyed annulus. This type of lesion does not usually cause pressure symptoms, but occasionally it is sufficiently large to produce symptoms similar to those of any growth at this site.

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PANCREAS, DISEASES

See also B.E.M.P., Vol. IX, p. 386; and Cumulative Supplement, Key Nos. 1203–1208.

Inflammatory conditions

Acute

Clinical and radiological features.—In acute disease the pancreas is swollen to two or three times its normal size and thus is produced radiological evidence of pressure against the greater curvature of the stomach. Metheny, Roberts and Stranahan record the evidence presented by a study of 32 cases of acute pancreatitis, including the clinical and radiological features.

In addition to elevation and flattening of the greater curvature, radiography may show increased size of the duodenal loop with loss of tone and ileus and tender tumefaction of the pancreas during fluoroscopy. The latter finding is pathognomonic. In a straight film with the patient supine, the characteristic outline of the stomach may often be seen. More frequently there are blobs of gas in the cardiac orifice and duodenal bulb. There may be increased density of the pancreatic area or localized ileus, especially of the transverse colon or upper loops of the jejunum. In all the cases studied by the authors, the disease had a sudden acute onset with nausea and vomiting, epigastric pain and negligible abdominal tenderness. Every patient had albuminuria. There was not the rigidity to suggest ruptured peptic ulcer and the patients were too ill to suggest an acute condition of the gallbladder. Slow pulse rates and normal blood pressures excluded the diagnosis of coronary thrombosis. Acute pancreatitis with associated ileus produces a silent abdomen and must therefore be differentiated from certain types of strangulated obstruction. In cases of pancreatic oedema the level of blood amylase remained high as long as the disease lasted but in those patients with pancreatic necrosis the amylase returned to the normal in about 2 days. The leucocyte and polymorphonuclear counts were higher in necrosis than in oedema and cyanosis was a common feature of the former. The authors consider that the acute phase of the disease is best treated by non-operative means and suggest that x ray therapy in small doses may be indicated.

Blood calcium—Edmondson and Berne report on observations on calcium disturbance in patients with acute pancreatic necrosis who were treated in Los Angeles County Hospital. Normal total blood calcium varies from 9 to 11 milligrams per 100 cubic centimetres of blood and the total amount of combined and diffusible calcium in the total blood of a normal adult of average weight is 650–700 milligrams. Post-mortem estimations of the total amount of calcium deposited in and around the pancreas were made in 6 patients who died from acute pancreatic necrosis, and from 100 to 1 732 milligrams of total calcium were found in the areas of fat necrosis. In a second group of patients measurements were made of the total blood calcium and diffusible and non diffusible calcium was measured in a third group. In 36 out of 50 cases of pancreatic necrosis serum calcium was found to be below 9 milligrams per 100 cubic centimetres some time between the second and fifteenth day of the disease and the average serum calcium value was lowest in the entire series on the sixth day. Serum calcium values below 7 milligrams indicated a fatal prognosis. Diffusible serum calcium was found to remain stable in spite of decrease in the total serum calcium.

Calculi

Clinical picture

Pancreatic lithiasis with fatal intestinal haemorrhage—Fanger reports on a case of pancreatic lithiasis complicated by fatal intestinal haemorrhage which masked the symptomatology and prevented clinical diagnosis. An elderly man, who had been treated 3 years previously for 'fatty liver' ascribed to alcoholism, suffered diffuse non localizing intermittent abdominal pain and lost 20 pounds of weight during the year prior to his admission to hospital. Occasional melaena terminated in passage of bright red diarrhoeic stools 2 days before he was admitted. Intermittent bleeding into the bowel continued. For 5 days the stools were clay-coloured. No glycosuria occurred. Sigmoidoscopic and x ray examination of the gastro-intestinal tract was unhelpful. Necropsy revealed a pancreatic calculus, 3 millimetres in diameter, which had eroded a small blood vessel at the base of an ulceration of the duodenal mucosa 4 millimetres in diameter, situated medial to the ampulla of the bile duct. This represented the orifice of a sinus tract terminating in a pancreatic duct and apparently was formed by inflammatory reaction evoked by the pancreatic calculi. Throughout the dilated pancreatic ducts were numerous friable calculi, most of which were small. Histologically the pancreas showed interlobular and intralobular fibrosis not involving the islands of Langerhans. The enlarged liver showed fatty infiltration. Fanger discusses theories of pancreatic calculus formation as yet unsubstantiated. A history of alcoholism appears to be significant. Ideally, diagnosis is by x ray demonstration of radio opaque calculi extending along the pancreatic axis. Lack of steapsin and lipase causes steatorrhoea. Hepatomegaly due to fatty infiltration. Deposition. Abdominal pain, partly attributable to overdistension of pancreatic ducts, is very variable in type and location.

Fistulae

The normal pancreatic secretion

Miller and Wiper base their study of the physiology of the pancreatic secretion on the detailed observation of 3 patients with external pancreatic fistulae. It was found that the general nutritional state of the patient was directly proportional to the severity of the fistula. The pancreatic outflow is continuous throughout the 24 hours. One patient produced 1,770 cubic centimetres of pancreatic juice in 24 hours. In this case the loss of sodium ion through the fistula had lowered the concentration in the blood and the patient showed a syndrome complex of great similarity to that found in experimental sodium deprivation and in Addison's disease. Alleviation of symptoms was obtained when adequate quantities of water and sodium and sufficient plasma protein to hold them in solution, were administered. Ionized calcium in the pancreatic secretion was found in approximately the same concentration as in the plasma and the authors stress the significance of the discharge of such quantities of calcium into the upper alimentary tract in calcium metabolism. The introduction of water,

sodium bicarbonate, magnesium sulphate, olive oil and glucose into the duodenum all diminished the flow of pancreatic fluid to an extent which varied according to the substance used. Hydrochloric acid promoted a marked outflow, and chicken broth an increase which was short lived. Water taken by the mouth, presumably owing to the washing of hydrochloric acid into the duodenum, increased the outflow; coffee decreased the flow. Sulphanilamide given by the mouth was found in the fluid in an approximately equivalent concentration as in the blood. The administration of 2,000 cubic centimetres of intravenous saline or of 5 per cent glucose increased the outflow. The subcutaneous injection of 1 cubic centimetre of 1 in 1,000 histamine acid phosphate caused a marked stimulation of the pancreatic juice.

Cysts

Signs and symptoms

Twenty-six cases reviewed.—Philipsborn, Lawrence and Lewis present findings in 26 proved cases of pancreatic cystic fibrosis, which causes a syndrome recently recognized as not uncommon. Symptoms commence usually in infancy as gastro-intestinal or respiratory disturbances or both. Chronic cough and coryza or failure to gain weight commonly occur. One out of every 4 or 5 patients will have had a sibling who died in childhood from diarrhoea, pneumonia or malnutrition. In the 26 of the authors' cases which came to necropsy, each pancreas showed increased intralobular and interlobular connective tissue and dilated ducts. Lung abscesses occurred in 23 cases. Emphysema and atelectasis were common; often *Staphylococcus aureus* could be cultured. Squamous-cell metaplasia of the tracheobronchial tree occurred in 14, liver steatosis in 17, keratomalacia and rickets each in 2 cases. The extreme variety in stools noted is considered to be due to fluctuations in enzymatic activity of gastric juice and succus entericus, which continues although pancreatic secretions are greatly reduced, and to varying intestinal absorptive and motile power. Serial studies of stools and estimation of vitamin A absorption curves from blood obtained before and after administration of Oleum Percomorphum proved to be helpful routine procedures. Vitamin A curves in patients with fibrocystic disease were flattened and at all times under 30 units—perhaps only a reflection of poor fat absorption. Analysis of duodenal drainage obtained after pancreatic stimulation by intravenous secretin, although diagnostic in the presence of achylia pancreatica, is too difficult to be practicable except in cases in which it is essential for diagnosis. Roentgenological examination aids diagnosis of pulmonary involvement. Philipsborn, Lawrence and Lewis describe a typical case which was diagnosed *ante mortem*, the significant laboratory findings being tabulated with those from a normal child and from one with coeliac disease. Diets high in protein and low in fat plus administration of oral pancreatic extracts and parenteral vitamin A in large doses, may control the gastro-intestinal disturbance. Prophylactic control of respiratory disturbances is essential.

Tumours

Carcinoma of pancreas

Clinical effect of neoplastic invasion of pancreatic nerves.—A study made by Drapiewski on the invasion by carcinoma of the endoneural and perineural spaces of the pancreatic nerves, and of certain other nerves in proximity to the pancreas, was based on 83 unselected cases of carcinoma of that organ taken from the necropsy and clinical records of the Mayo Clinic for the period from 1931 to 1941 inclusive. It was found that the pancreatic nerves were invaded in 84 per cent and that the incidence of pain was 76 per cent in those 83 cases. It is suggested that neural invasion may be one cause of pain, although it is true that peritoneal irritation or tension, as well as dilatation of the biliary passages, may also cause pain. Jaundice occurred in 71 per cent of the cases and the common bile ducts were found to be patent in 25 jaundiced patients. It was therefore considered that a physiological block resulting from invasion of the wall of the duct occurred, with consequent inhibition of the contractive power of the common duct. The suggestion was supported by the fact that there was neoplastic invasion of the wall of the duct in most of the jaundiced patients with a patent common duct. There seemed to be no significant association between metastasis elsewhere and neural invasion, and no correlation was found between the grade of malignancy and the frequency of neural invasion.

Rupture

Treatment

Keynes describes 2 cases of the rare condition of rupture of the pancreas unassociated with injury to other viscera. One instance was due to direct violence, the other probably to underwater concussion resulting from explosion of a depth charge. In the first case, after laparotomy and drainage the fistula closed, but a large pseudocyst formed 3 months later; this was opened and drained, leaving a fistula. Pancreatico-jejunostomy was performed by the Lahey and Lium technique. The patient appeared to be well for about 2 months and then signs of acute peritonitis developed. Laparotomy showed mild peritonitis; the site of anastomosis was sound. Except for a pulmonary embolus which nearly caused his death, the patient remained well for 4 months but then there developed attacks of nausea and retching. A barium meal examination showed some deformity of the first part of the duodenum but no other abnormality in the intestinal tract. The second patient, when floating upright in the sea supported by his Mae West belt, experienced a "rumbling in the belly" when a bomb exploded in the conning tower of a sinking submarine, about four hundred yards away. He was quite positive

that he was uninjured when the aeroplane of the crew of which he was a member crashed into the sea. Laparotomy and drainage was performed with temporary benefit but later a second operation was necessitated and the lesser peritoneal sac was found to be tensely filled with fluid and to be obstructing the colon. The condition was relieved but 10 days later laparotomy was again performed for a volvulus of the small intestine originating in an adhesion of intestine to the root of the mesentery. Subsequent recovery was uneventful.

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Philipsborn, H F, Jun, Lawrence, G, and Lewis, K G (1944) *J Pediat*, 25, 284

PENIS AND SCROTUM DISEASES

See also B E M P, Vol IX, p 498

Penis

Congenital abnormalities

Congenital phimosis—Birnie states that the usual operation of circumcision consists either of a dorsal slit or of amputation of the prepuce. In these procedures both skin layers of the prepuce are incised simultaneously, including the connective tissue and blood vessels. The author disapproves of the technique, since it may result in complications such as haemorrhage, oedema and malformation. It is recommended that toothed forceps should be used to pick up the skin of the outer preputial layer. A small slit is made at this point. The blades of a pair of blunt-ended straight scissors are introduced through the slit and opened. By alternately pushing the scissors forward and opening them the surgeon can easily separate the skin from the connective tissue without injuring the latter. The process of separation is facilitated if the foreskin is fully retracted and kept tense. Any constriction is cut from within outwards, avoiding injury to the connective tissue. The flaps of skin to be removed may be of any size or shape to suit the preference of the surgeon, but both skin layers should never be cut at the same time. The method is worthy of careful consideration, especially in operations on adults.

Tumours

Case of sarcoma—Levant describes a case of sarcoma of the penis in a negro, aged 29 years. The tumour was stony hard and was situated in the right corpus cavernosum. The urethra and overlying skin were not involved. Biopsy confirmed the diagnosis but this method of investigation precipitated a copious haemorrhage 8 days later. The patient objected to amputation and deep x ray therapy was instituted. Improvement did not occur with concentrated therapy but fractional doses resulted in the complete disappearance of the tumour 9 months later. Metastasis in a lymphatic gland, however, produced a painful ulcerating mass in the left inguinal region and general systemic failure ensued. In 1924 Joelson gave an account of a patient with this condition and reviewed 35 cases in the literature. All these tumours involved the corpora cavernosa in boys or young men and the pathological groups consisted of fibro-sarcoma, round-celled sarcoma, melanosarcoma and endothelioma. Foulds and Flett in 1938 reported a case of endothelioma of the corpora cavernosa but only 6 other cases could be traced in the literature from 1883 to 1938. The authors consider that the tumour originates from the cells which line the blood spaces of the corpora cavernosa.

Birnie, J M (1945) *New Engl J Med*, 232, 218

Levant, B (1944) *J Urol*, 52, 63

PEPTIC ULCER

See also B E M P, Vol IX, p 504, and Cumulative Supplement, Key Nos 1236 and 1237

Peptic ulcer of stomach and duodenum

Aetiology

Gastric ulcer and duodenal ulcer compared—Tidy examines the admissions to St Thomas's Hospital, London to ascertain the trend in the incidence of peptic ulcer for the periods 1910-1913 and 1922-1937. Gastric ulcer and duodenal ulcer are considered separately with subdivisions for sex and age. In the former period the ratio of gastric to duodenal ulcer was 2.2:1, the sex ratio being 0.6 male:1 female. In the latter period the ratio of gastric to duodenal ulcer was 1.9:1 and the sex ratio was 2.6 gastric and 8.4 duodenal in males:1 in females. Ages over 40 and ages under 40 years are grouped. The trend of gastric ulcer in males over 40 rose slowly from 1910-1913 to 1922-1925 then rapidly to more than double in 1926-1929 and remained at this level. The same trend was seen, but at a much lower level, in males under 40 years of age. The trends for the two age groups for duodenal ulcer were close together as plotted on the graph. In females there was a spectacular fall in admissions to hospital for gastric ulcer under the age of 40 and only a slight increase over that age. The ratio of gastric to duodenal ulcer changed in the course of years. The incidence of gastric ulcer in males gained over that of duodenal ulcer before 1930 because of more rapid increase and after 1940 by remaining stationary while the incidence of duodenal ulcer was falling. The ratio of

gastric to duodenal ulcer rose for males and fell for females in both age groups. Admissions of males under 40 years of age with gastric ulcer first and finally became in excess over admissions for duodenal ulcer, in 1929. In the period 1922–1937 admissions were highest in the decade 40–50 years for both types of ulcer and for both sexes. It is suggested that there is more than one group of aetiological factors producing gastric ulcer and that they operate at different ages and have different effects in the two sexes.

Course and prognosis

Vital statistics of a 20-year period.—Morris and Titmuss review the vital statistics regarding peptic ulcer for the period 1921–1941. For the 10 years before the recent war, more than 43,000 deaths from peptic ulcer were registered in England and Wales. The mortality rate of peptic ulcer in men was then rising and has been accelerated since the outbreak of war. Discharges from the army up to the end of 1915 for “inflammation and ulceration of the stomach” were 709. In the recent war up to the end of 1941, discharges on account of peptic ulcer numbered 23,574. From the age of 35 years onwards, male mortality increases and is doubled after the age of 45. In females under 55 years of age there is a decline and only a slight rise between the ages of 55 and 75. It is the increase in the mortality in males that prevents a decline in the death rate of men of 45–65 years. Social and occupational factors are examined in regard to peptic ulcer mortality. Up to the age of 55, mortality of gastric ulcer rises in a regular manner as the social scale descends. With duodenal ulcer there is little difference. Duodenal mortality after the age of 55 and gastric mortality after 65 both decline with descent in the social scale. Between the ages of 35 and 70 the rate in male mortality in London is twice that in rural areas. Mortality in both sexes from gastric ulcer is higher than from duodenal ulcer which is seen perhaps three or four times as often in practice. Peptic ulcer in men is extending at both ends of life.

Treatment

Cure of ulcer: the psychosomatic basis.—Reviewing the present status of the treatment of uncomplicated duodenal ulcer, Morlock stresses throughout the psychosomatic aspects of the condition. The neurogenic factor is the most important single aetiological factor in many cases in which hyperirritability, restlessness and emotional instability exist. Mental readjustment will often reduce the psychic stimuli to the secretion of gastric acid which may be more powerful than the chemical or hormonal stimuli. In general, Morlock considers that an initial fortnight's treatment in hospital is the ideal, so that strict dietary supervision and detailed instruction can be undertaken. The Sippy programme is often blamed for failures in treatment by those who interpret it as a bland diet and the administration of alkalis and forget that Sippy insisted on detailed hospital care, frequent nightly aspirations of hyperacid gastric juice and daily psychotherapy. Hospital treatment of an active ulcer should be started with a diet of milk and cream, 4 ounces every hour from 7 o'clock in the morning until 9 at night, with an antacid between feeds. Aluminium hydroxide gel and magnesium trisilicate can be used fully without risk of alkalosis. One of the most valuable medicines in treatment is the sedative. By the time he leaves hospital the patient is usually ready for a liberal diet of 3 bland meals a day with an intermeal and bedtime feeding of milk and antacid 6 or 8 times in 24 hours. Night treatment by means of sedatives and long-acting antacids, intragastric drip therapy, or the waking of the patient by alarm clock for feed or alkali, is of the utmost importance. Morlock considers that tobacco should be given up. After complete control of symptoms for 2 years the lesion may be considered to be quiescent and the patient should by then be educated in the prevention of factors leading to reactivation.

Aluminium phosphate gel.—Lichstein, Simkins and Bernstein believe that aluminium phosphate gel is of value in the treatment of peptic ulcer. The dosage of the preparation is 30 cubic centimetres of a 4 per cent solution 3 times daily, after meals, at bedtime and whenever necessary during the night for the relief of pain. The authors gave the drug in this dosage to 22 patients with peptic ulcer. In 15 cases the disease was complicated by haemorrhage, but the treatment resulted in the disappearance of occult blood from the stools in an average of 6 days. In contrast, occult blood persisted for an average of 10 days in a group of 15 patients with bleeding ulcer treated by various other methods. Moreover, radiographic examination showed comparatively rapid healing in patients treated with the drug, especially in the case of uncomplicated ulcer. It is suggested that larger doses would have produced even better results. The aluminium phosphate gel promptly relieved pain and had an excellent effect on appetite. It was much less constipating than was the hydroxide gel. In several patients nocturnal pain was persistent, but it was readily controlled by increasing the dose of the phosphate gel at bedtime or by the employment of the intragastric drip method. The drug produced a moderate reduction of free hydrochloric acid and total acidity. Blood tests indicated no change in the metabolism of calcium and phosphorus, and no effect on the increase of blood urea nitrogen commonly observed in bleeding peptic ulcer. In the course of the investigation the findings of Lyons and Brenner were confirmed, since it appears that the erythropoietic response to peptic ulcer associated with haemorrhage is determined by the degree of anaemia found at the time of the examination of the patient.

General review of modern methods.—Divergent views are expressed on the treatment of duodenal ulcer. Walton thinks that the one indication for surgical interference is the failure of medical treatment. His routine treatment of duodenal ulcers, whether or not causing stenosis, is posterior gastro-enterostomy, and he reserves partial gastrectomy for the 4 per

cent in whom gastrojejunal ulcer has developed. Marshall holds that mental and physical rest, the common factor in all regimens, is the basis of medical treatment, which he regards as primary. He stresses the importance of distinguishing between cure of symptoms and cure of the ulcer which persists long after disappearance of radiological signs and occult blood. Hydrochloric acid estimation Marshall considers to be unreliable in estimating progress and prognosis. Evans questions the value of test meals in relation to duodenal ulcer. He considers that medical treatment is basic, and reserves surgery for selected cases; he emphasizes that phenobarbitone is more important than are alkalis since mental relaxation is essential. Frequency, rather than composition, of feeds is important and adequate quantities of carbohydrate, iron and ascorbic acid are essential. Tidy points out that although a first course of medical treatment may fail, a second is often successful and that a form of medical treatment condemned as unsuccessful by surgeons may have been one which would not have satisfied a physician. He advocates periodical discussions of relative merits of medical and surgical treatments and thinks after treatment at least as important as initial treatment. Pannett is astonished at an experienced surgeon's opinion that uncomplicated intractable duodenal ulcer is a medical disease since suitable operation completely transforms a patient's outlook on life. He has abandoned the Billroth I anastomosis for an operation of the anterior Polya type. Taylor advocates gastroscopic estimation of the degree of rugosity in the stomach since he considers hyperrugosity to be an indication for gastrectomy because it predisposes to stomal ulceration.

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PERITONITIS: ACUTE PERITONITIS

See also B E M P, Vol IX, p 537, and Cumulative Supplement, Key No 1241

Morbid anatomy

Extension of disease

Findings in experimental dogs—Steinberg and Martin produced experimental infections of the peritoneum in dogs by ligation of the appendix followed by injections of air into its lumen. In some cases castor oil was given for the purpose of increasing tension on the wall of the bowel. The authors found that a peritoneal infection diffuses through the peritoneal cavity fairly promptly after perforation of the bowel takes place and that the spread of the infection is uniform throughout the cavity except for two areas in which it is increased, namely the surface of the perforated bowel and the right subdiaphragmatic area. They state that the diffuse peritoneal involvement is not inimical to the body since it represents an extensive defence surface from which bacteria are removed to which great numbers of phagocytic leucocytes are attracted, and which aids the passage of a large number of bacteria through the capillary vessels and lymphatic channels. The resulting bacteraemia is transient because the bacteria are deposited eventually in the various viscera for disposal by the reticulo endothelial system. Bacteraemia in peritonitis is associated with survival whereas the retention of micro organisms in the peritoneal cavity results in death. Microscopical examination of the exudate offers a simple and valuable method of diagnosis and prognosis of peritoneal infections. The right subdiaphragmatic region and the area of the perforated bowel do not represent the condition which exists in the general peritoneal cavity; this is reflected much more in exudate from other regions including the midabdomen. The authors point out that these deductions are contrary to existing conceptions of peritonitis spreading from a focus, with the body attempting to hold back the onrushing flood. They suggest that the pools of exudate amid relatively normal peritoneum, which are often found at operation, represent an end result and not the initial method by which the peritoneum deals with its bacterial invaders.

Treatment

Curative

Intraperitoneal administration of sulphonamides—The intraperitoneal application of sulphonamide compounds has provided the first successful method of combating peritonitis by direct attack and has thereby lowered the mortality rate in acute abdominal conditions. From his experience Gardiner concludes that primary peritonitis—which is caused by a paratively uncommon is very lethal and unresponsive to chemotherapy and should, therefore, still be treated on expectant rather than on operative lines. In secondary peritonitis, however, —usually due to the normal inhabitants of the gastro intestinal tract—the sulphonamides, owing to their non specificity, exercise a bacteriostatic effect on most of the organisms found in such mixed infections although the different bacterial groups show marked variation in their susceptibility to sulphonamide therapy. To be really effective when used intraperitoneally, the compound must be absorbed slowly and be capable of dealing with the infecting agent without producing deleterious effects. Sulphapyridine came nearest to fulfilling these conditions. The average dose required was found to be 15 grammes of the sterilized powder,

although since the effectiveness of the compound is much reduced in the presence of pus, when profuse suppuration is present as much as 25 grammes may be used in order to obtain a higher concentration. The substance should be applied by dusting or, preferably, as a fluid suspension squirted by means of a syringe into the peritoneal cavity and, when drainage is instituted, down the tube. In this way the powder cannot be rapidly walled off by the peritoneum as happens if it is simply "dumped". Complications such as toxic reactions, intra-abdominal adhesions or delayed healing were negligible. The data were obtained from some 50 cases, mostly of appendicitis, but encouraging results were also obtained in certain cases of intestinal obstruction which necessitated bowel resection.

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PHARMACOLOGY

PHARMACOLOGICAL EFFECTS OF SINGLE DRUGS

Alloxan

Effects on islands of Langerhans

The specific effect of alloxan on the pancreatic islands of Langerhans is reported on in detail by Bailey, Bailey and Hagan. Rabbits were given intravenous injections of 200 milligrams of alloxan per kilogram of body weight. Examination of the islet cells as early as 5 minutes after the injection showed commencing degeneration, in the β cells especially. After 2 hours, distortion of the general architecture of the islands was more clearly seen. Examination during the hypoglycaemic phase showed a progression of the earlier lesion and at 5 hours coalescence of the islet cells was occurring and some of the cells had disintegrated completely. A number of α and non-granular cells at the periphery were unaffected throughout. At no stage was there neutrophil infiltration. No alteration in the pathological lesions occurred which could be correlated with the rapid initial drop in blood sugar. Thus in a fully developed alloxan diabetes there was loss of all β cells, persistence of a few α and non-granular cells and absence of detectable injury to external secretory tissues. Several months after the establishment of diabetes the total number of islands was small, those which survived being composed of masses of cells resembling α cells. Injections of small repeated doses of alloxan showed irreversible changes in a predominating number of the islet cells and reversible changes in others. Changes in organs other than the pancreas were minimal. Thus the lesion produced in the islands of Langerhans in the rabbit after a single dose of alloxan is degenerative throughout, notwithstanding the different phases of the blood sugar curve. It is possible that the cause of the hypoglycaemic phase is release of preformed insulin.

Amphetamine sulphate

Effects of benzedrine and of alcohol compared

Finkelstein, Alpern and Gantt describe experiments with amphetamine sulphate on healthy young adults. In these subjects 10–15 milligrams of amphetamine sulphate produced a rise of 8 millimetres in the systolic blood pressure. The rise was doubled with a dosage of 20–30 milligrams. There was likewise a rise in diastolic pressure of 6 millimetres and 12 millimetres, respectively. No change occurred in the resting pulse rate, but there was an increase in the resting respiratory rate. The threshold of sensation to an electrical shock and the acuity of hearing at all pitches were unchanged. Tests of motor conditional reflexes showed a slight improvement in the differentiation between positive and negative conditional stimuli. There was no alteration either in the respiratory conditional reflex or in the ability to perform the number series completion test. To test the conditional reflexes electrical shocks, controlled by switches, were used in conjunction with auditory and visual stimuli. The results were recorded on a kymograph. The drug produced a change in mood, and most of the subjects became more cheerful, alert and talkative. The use of amphetamine sulphate by armed forces under periods of stress gives a special significance to the fact that the general improvement in mood was unaccompanied by impairment of performance. In comparison, administration of ethyl alcohol had a pronounced effect on the motor conditional reflexes. Alcohol favoured excitatory reactions and interfered with inhibitions. The respiratory conditional reflex was impaired, and there was an increase in the threshold for perception and for pain. Very little difference in performance was detected with the number series test even after a dosage of 2 cubic centimetres per kilogram. This proves that, as an indicator of cerebral cortical activity, the conditional reflex test is to be preferred to the number series test.

D.D.T.

Penetration into skin

Draize, Nelson and Calvery have studied the skin penetration of D.D.T. (2 : 2-bis(*p*-chlorophenyl) 1 : 1 : 1-trichloroethane) in laboratory animals. Exposure to relatively large doses of undiluted D.D.T. in powdered form did not produce any symptoms of poisoning in animals with either intact or abraded skin. Solutions in a non-irritant solvent such as dimethylphthalate were absorbed by both intact and abraded skin and caused severe poisoning especially when used by inunction over long periods. Guinea-pigs, rats and rabbits were very susceptible to the effects of this method but dogs were little, if at all, affected. Signs of toxicity included severe anorexia, loss of weight, hyperexcitability and eventual clonic convulsions. When death occurred it was the result of secondary infection after the emacia-

tion Severely poisoned animals exhibited a moderate leucocytosis with a characteristic increase in the percentage of heterophils The authors consider that solutions of DDT are mildly irritating to intact and abraded skin and that from solutions DDT is absorbed and is a severe systemic poison A number of preparations containing DDT in concentrations up to 5 per cent may however be safe for limited use No irritation occurs from powdered DDT when applied by patch tests or on the hands of operators having daily contact with it for periods up to one year Although knowledge of the efficacy of DDT as an insecticide is the result of relatively recent entomological research it was synthesized by Zeidler as long ago as 1874

Desoxycortone acetate

Effect of desoxycortone and of sodium chloride on blood pressure

Perera and his colleagues report observations on the effect on the blood pressure of sodium chloride and of desoxycorticosterone acetate (desoxycortone acetate) The first series of cases consisted of patients with hypo adrenalism Fifteen patients were maintained in electrolyte balance with a normal blood volume on daily oral doses of sodium chloride for an average period of more than 3 years and no significant hypertension developed Desoxycorticosterone acetate was given to 24 patients for an average period of 2 years and 12 of these showed repeated blood pressure readings in excess of 140/90 It was noted that 8 patients with the hypertensive reaction gave no history and presented no signs or symptoms to suggest previous or coincidental cardiac, vascular or renal disease The pressor effect of desoxycorticosterone acetate was also demonstrated in 3 subjects without disease of the suprarenal glands The time of appearance of hypertension could be measured in weeks or months rather than in days The development of hypertension could therefore not be ascribed to the restoration of the electrolyte and fluid balance to the normal in patients with previous suprarenal insufficiency In such cases restoration occurs promptly when acute hypo adrenalism is treated with adequate salt and replacement therapy The investigators did not find any correlation between positive cold pressor tests and the appearance of hypertension thus demonstrating that a labile vascular system was an unlikely determining factor Progressive arteriolar changes did not develop but it seems to be probable that desoxycorticosterone acetate acts directly or indirectly on the peripheral vascular system

Dibutoline sulphate

A new mydriatic and cycloplegic drug

Swan and White describe a new mydriatic and cycloplegic drug named dibutoline sulphate (the dibutylcarbamate of dimethylethyl β hydroxyethyl ammonium sulphate) It is readily soluble in water and since in saline or buffer solutions it forms salts likely to cause conjunctival irritation it should be dissolved in distilled water Heat and light decompose the solution but it is stable at room temperature Partially decomposed solutions lose potency but are non toxic Dibutoline paralyses the ciliary muscles and the sphincter of the iris but not the smooth muscle of the lid or the dilator fibres of the iris Its mydriatic effect can be enhanced by administration of epinephrine (adrenaline) or related compounds It is a more effective cycloplegic than is homatropine the mydriasis and cycloplegia which it produces develop and disappear simultaneously The onset and duration of its action as compared with those of homatropine were studied on the eyes of more than 100 patients One drop of 5 per cent solution of dibutoline sulphate usually induced mydriasis and cycloplegia in 12-20 minutes reaching a maximum in 40-55 minutes The commencement of the effect usually preceded that of homatropine by 10-15 minutes Visual disability after the use of atropine and scopolamine (hyoscine) lasted from three to ten times longer than did that due to dibutoline Repeated instillations of dibutoline cause conjunctival irritation and transitory type of dermatitis and conjunctivitis were not observed Dibutoline facilitates corneal penetration by and thus enhances the effect of atropine patients resistant to the one drug respond to the other Dibutoline has potent action upon organisms commonly causing ocular inflammation and enhances corneal penetration by the sulphonamides

Diodrast

Its influence on uric acid clearance

Bonsnes, Dill and Dana state that the values now obtained for uric acid clearances average about 15 cubic centimetres per minute Other investigators using different methods have reported clearances of the same order of magnitude Much greater uric acid clearances were obtained previously and the discrepancy is due to the fact that the earlier tests were made on patients receiving Diodrast (diodone) This substance is excreted by the renal tubules and is believed to inhibit the reabsorption of uric acid Experiments were performed on 11 normal women in the first week of the puerperium Sufficient water was given to ensure adequate diuresis The first specimen of urine was obtained by catheterization and was discarded The urine was then collected for two consecutive periods of half an hour and a specimen of blood was taken after the first half hour Data obtained from the examination of these specimens gave a mean uric acid clearance which averaged 14 ± 2.9 cubic centimetres per minute On the next day the same procedure was carried out but in addition an intravenous injection period It was then found that the amount of clearance at the beginning of each half hour period but the effect on the excretion of urea and creatinine was unaltered Injections of

hypertonic solutions of glucose exerted no effect on the excretion of uric acid, and the clearances were not significantly different from those obtained with water diuresis.

Gramicidin S

Effect on various bacteria

During a systematic investigation of antagonistic sporulating bacilli, Gause and Brazhnikova found one organism of the *Bacillus brevis* type which would, in culture, constantly kill staphylococci. From it has been obtained a new bactericidal polypeptide, gramicidin S, the chemistry of which is studied by Belozersky and Passhina. The bacteria are grown on yeast and glucose. The culture fluid is acidified after incubation, the supernatant fluid is removed, and the concentrated sediment is dried, ground, made into alcoholic solution and filtered. Gramicidin S, when obtained in pure crystalline state, has a melting point of 268–270° C. and a nitrogen percentage of 13, and gives a positive biuret reaction. It is different chemically from other known crystalline polypeptides produced by aerobic sporulating bacilli, such as gramicidin Dubos and tyrocidine hydrochloride derived from tyrothricin. It has a greater range than the latter and is effective against Gram-negative bacilli such as *Escherichia coli*. Although more effective in killing staphylococci, gramicidin S is less active than is tyrothricin against streptococci and pneumococci. It is not toxic and is harmless when applied locally or in cavities. It is stable and its antibacterial activity is not destroyed by autoclaving. It is effective in protecting animals against anaerobic infection by *Clostridium perfringens*. Sergiev records results of treatment of 1,500 patients with gramicidin S. Cases of suppuration of soft tissues, mostly necrotic, from gunshot wounds, severe burns, abscesses of the abdominal wall and anaerobic infections, were treated with watery solutions; bacteria usually disappeared from the wounds in 5 days; thereafter gramicidin ointment was used and rapid epithelialization ensued. Osteomyelitis, peritonitis and empyema responded well. An average of 4.1 days was necessary for healing 117 cases of contagious impetigo. Although only a small number of cases so far have been studied, all wounds treated prophylactically with gramicidin S healed by first intention. A characteristic feature of the substance is its power to alleviate pain.

Morphine

Antidiuretic action

Among its other effects, morphine has been presumed to exert an antidiuretic action, but the output of water may also be restricted by the sleep-producing, thirst-abolishing and gastric effects of the drug. In a series of carefully controlled experiments in dogs, de Bodo has investigated the antidiuretic action of morphine and its mechanism. When normal dogs in the postabsorptive state and in water equilibrium are given water, either by the stomach or by slow intravenous infusion, they excrete within 3 hours an amount practically equivalent to that taken. When given by the stomach, the water is completely absorbed from the gastrointestinal tract in 40 minutes. When morphine is given 40 minutes after the administration of water by the stomach or 15 minutes before intravenous infusion, water diuresis is markedly inhibited. Morphine, however, either does not inhibit saline diuresis or inhibits it to a lesser degree than it does water diuresis. Morphine does not inhibit water diuresis in dogs with diabetes insipidus. It inhibits water diuresis only if a functioning neurohypophysis is present in the animal to furnish the antidiuretic hormone and normally this is liberated by the action of morphine on the hypothalamico-hypophysial system. Although morphine causes liberation of adrenaline it is not the action of the latter in producing renal ischaemia which is the cause of morphine antidiuresis, since the effects are identical in adrenal-inactivated dogs. Experiments also show that morphine does not potentiate the antidiuretic action of the circulating hormone of the posterior lobe of the hypophysis. The relationship of acetylcholine to morphine antidiuresis is not yet determined.

Effect of additional administration of dextroamphetamine

Ivy, Goetzl and Burrill describe an experiment undertaken for the purpose of determining whether or not the administration of dextroamphetamine with morphine sulphate influences the analgesic effect of morphine. The experimental subjects were 21 healthy medical students. Sixteen milligrams of morphine sulphate and 20 milligrams of dextroamphetamine were given. Sixteen subjects received morphine alone and 17 the combination of drugs, 12 of the subjects serving twice. The pain threshold was determined by measuring the voltage necessary for the production of pain when an alternating current was applied to metal filling in a tooth. It was found that the combination of drugs had a greater analgesic effect than had morphine alone. Using a flicker fusion test the authors found that the effect of the combination of drugs, as compared with that of morphine alone, delayed the drop in the flicker fusion threshold by 30 minutes. The choice reaction time, 150 minutes after the injection, was nearly four times greater in the morphine group of 8 subjects than in the 8 subjects who had had the combination of drugs. The combination of drugs caused a pronounced rise of blood pressure in all but one case. Morphine alone in 16 subjects caused a fall of pulse rate, but the combination of drugs caused an increase in 12 cases and a fall in 5. Nausea and vomiting were less frequently encountered—but not significantly so—after administration of the two drugs. Weakness and drowsiness and dizziness, although not objectively measured, appeared to be decreased by the addition of dextroamphetamine. Uniform results in all subjects were not produced by either morphine or the combination of drugs. The authors consider that from the subjective and objective evidence, on the average the addition of dextroamphetamine increases the analgesic effect of morphine and decreases the depressive. Undesirable side-

effects are probably delayed as well as counteracted. Ivy, Goetzl and Burrill conclude that this combination of drugs should be clinically investigated. Owing to the effect of dextroamphetamine on the blood pressure of some subjects a dose larger than 20 milligrams should probably not be used. Its use would be contra indicated in conditions of hypertension and delirium.

Nicotine

Vasoconstrictor influence in human beings

Roth, McDonald and Sheard describe experiments made in order to determine the vasoconstrictor effect of tobacco on the human circulation. A review of the literature on the subject showed lack of agreement among the investigators. Observations were made on 6 normal subjects all of whom smoked and inhaled habitually. Standard cigarettes were used with corn silk cigarettes, French ashless cigarette papers and a British filter holder as controls. The subjects when resting and supine and wearing thin pyjamas, smoked 2 standard cigarettes and a decrease in the cutaneous temperature of the extremities was observed. This did not occur with corn silk cigarettes but did so with the other controls. The decrease also occurred after 2 standard cigarettes had been smoked when the subjects were fully clothed and sitting or slowly walking. The basal metabolic rate increased when 2 standard cigarettes were smoked, but decreased with the corn silk controls. Electrocardiographic tracings showed an increase in heart rate and a lowering of the amplitude of the T wave with standard cigarettes but not with corn silk cigarettes. The subjects were given saline intravenously and then 2 milligrams of nicotine were added without their knowledge. This caused considerable reduction in cutaneous temperature and the electrocardiographic tracings showed definite increase in heart rate and lowering of the T wave. When 2 standard cigarettes were smoked and 2 milligrams of nicotine were given intravenously there was an increase in blood pressure and pulse rate but this did not occur with the corn silk controls. The cold pressor test was inconclusive, some subjects react excessively to cold and to tobacco. The decrease in cutaneous temperature continued for from half an hour to one hour after smoking ceased. Blood pressure, pulse rate and electrocardiogram returned to normal within 5-15 minutes. This suggests that the smoking of standard cigarettes should be avoided by persons with peripheral vascular disease and by wounded persons with arterial haemorrhage and who may be sensitive to tobacco since the added vasoconstriction may cause irreparable damage.

Ouabain

Electrocardiograms in normal persons after ouabain administration

Apter, Ashman and Hull report on the results of a quantitative study of the effects of intravenous administration of ouabain upon the electrocardiograms of persons without heart disease. The determinations made were the mean minute heart rate, the P-R interval, the Q-T interval, the direction and magnitude of the mean manifest QRS complex, the magnitude and direction of the ventricular gradient and the net area of the ventricular complex QRS-T in lead C4F. The ventricular gradient is the electrical effect, as projected on to the frontal plane, of differences in the rate of repolarization of different regions of the ventricular muscle. All effects from the drug were maximal at half an hour, and all traces had disappeared 48 hours after injection. In most individual cases there was no clear correlation between the dosage of ouabain and change in heart rate, but comparison with controls suggested that the drug, in increasing doses, produced in some cases an increasing diminution of average rate. In only 1 case was there a change in the P-R interval due to the drug. The Q-T interval was shortened by a 1.5 milligram dose in every case although not to a very significant extent (0.034 second). No changes in the QRS complex were observed. Progressively greater diminution of ventricular gradient was demonstrated with increasing dosage. On the average, in adults, the net area of QRS-T in lead C4F was reduced by about the same percentage as the magnitude of the gradient. Directional changes of the ventricular gradient, determined half an hour after a 1.5 milligram dose, were not apparent in 12 subjects and occurred to the left in 12 and to the right in 4. The authors state that it is impossible to express opinion regarding the constancy of the effect of ouabain upon the net electromotive force developed by the heart.

Paraldehyde

Dangers of residue at bottom of carboy container

Hemphill and Heller report the occurrence of toxic reactions to the administration of 120-minim doses of paraldehyde in 7 out of 9 female mental patients. These doses were made up from the residue at the bottom of the carboy container. Later about 6 ounces of this residue were made up to 20 ounces with fresh paraldehyde forming the suspect sample in the toxicity tests on mice. The patients were completely drowsy, could be roused only with difficulty 12 hours afterwards, speech was slurred and headache, giddiness and nausea were complained of. Tests with suspect paraldehyde and with fresh paraldehyde showed that smaller doses of the former were lethal to 50 per cent of the mice, it is reasonable to assume that the non-A chemical analysis indicated the presence of impurities as compared with the British Pharmacopoeia 1932 standard. Overdosage and idiosyncrasy being ruled out, the toxic reactions are attributed to unknown chemical products of decomposition. The authors comment on the rarity of recorded cases of "paraldehyde poisoning" in consideration of the widespread use of the drug, and support the plea that a suitable preservative be officially added for the purpose of preventing chemical decomposition.

Penicillin

Landmarks in development

Fleming² states that his discovery of penicillin took place in 1928 when a spore of *Penicillium notatum* settled on a culture plate of staphylococci. The mould grew and induced a dissolution of the colonies of bacteria for a considerable distance around the point of growth. Subsequently it was proved that the mould produced a substance which had bacteriostatic, bactericidal and bacteriolytic properties. This substance did not give rise to toxic effects either in man or in mice. It was readily diffusible in agar and was non-toxic to leucocytes. At first the crude penicillin was employed in the laboratory for the purpose of isolating insensitive microbes from a multitude of sensitive bacteria. Unfortunately the preparation was not sufficiently stable to be used as an antiseptic. In 1930 Raistrick and his collaborators found that the mould would make penicillin in a simple synthetic medium containing a few salts and some glucose. Most of the attempts, however, to concentrate penicillin ended in the destruction of the substance. The work on penicillin was continued in 1938 by Chain and Florey, who used Fleming's culture and Raistrick's medium. The substance was extracted rapidly at a low temperature with ether in acid solution, and salts were prepared which could be dried and rendered stable. Another advance was made when Coghill discovered that the addition of corn steep liquor—a byproduct of the Indian corn industry—to the medium produced a tenfold greater yield of penicillin. In 1942 Fleming used the drug for the purpose of curing a case of streptococcal meningial infection. This was the first patient to receive intrathecal injections of the preparation. Furthermore, it was the first case in which penicillin assays of the blood were carried out satisfactorily. At present the sodium salt of penicillin is used extensively but many workers have shown that the calcium salt can be substituted for all purposes.

Importance of bacteriological tests

Fleming³ considers that bacteriological tests are essential for successful treatment with penicillin. The agar diffusion method is employed in order to estimate the potency of the various preparations of the drug. An agar plate is planted with a sensitive organism, usually a staphylococcus, and the penicillin is placed in an agar cup or a porcelain ring. The penicillin rapidly diffuses into the agar and inhibits the growth of the staphylococcus over an area depending upon the strength of the preparation. Alternatively, the potency may be tested by making serial dilutions of the penicillin in broth infected with staphylococci. The end point is either the last tube to show complete inhibition or the first tube in which growth appears. These methods may be used for the purpose of examining other body fluids and of testing the sensitivity of organisms to penicillin. In order to estimate the penicillin content of blood serum it is necessary to make serial dilutions of the serum in physiological saline and to add group O blood infected with haemolytic streptococci. The mixtures are incubated in sealed capillary tubes and, after incubation, are examined for haemolysis. In most cases specimens of pus can be centrifuged, and the supernatant fluid can be tested in exactly the same way as can blood serum. The penicillin content of sterile urine may be assayed by means of any one of the three methods which have been described. Penicillin is destroyed by penicillinase, a substance which is elaborated by many bacteria. The antagonism between the two substances can be demonstrated by titration or by agar diffusion. The latter process is employed in order to ascertain whether an organism is or is not an effective producer of penicillinase. In making cultures from patients treated with penicillin, excess of penicillinase may be added to the medium or to the specimens of the body fluids.

Bigger's contention challenged

Garrod considers that a favourable environment enables penicillin to cause the death of bacteria fairly rapidly. It seems probable that, above a certain necessary minimal rate, disinfection by pure penicillin is unaffected by increase of concentration. Disinfection is retarded, however, by an increase in the amount of impure material in the sample. A concentration of 1 unit of penicillin per millilitre is not only just as effective as is one of 1,000 units, but also often more so. The only good reason for using strong solutions in local treatment is to ensure that loss by escape, dilution or absorption shall not permit the concentration to fall below the minimal level for full effect: about 0.1 unit per millilitre. The action of the drug is progressively impaired by an increase in the acidity of the medium between hydrogen ion concentrations of 7 and 5. A low pH in an inflammatory exudate may impair the action, a factor worthy of study as a possible cause of failure in treatment. Bigger's hypothesis that penicillin acts only on dividing cells is supported by the action of the drug on *Staphylococcus aureus* in diluted broth and in the presence of bacteriostatic agents such as boric acid, sulphathiazole and low concentrations of proflavine. On the other hand, there are two experimental findings which indicate that the behaviour of penicillin differs in no qualitative sense from that of other disinfectants. First, the disinfectant action on young cultures of *Staph. aureus* is much the same as in the case of very old cultures, and secondly the action is accelerated by an increase of the temperature throughout the range 4–42° C. The experiments therefore do not entirely support Bigger's contention that, if sterilization is to be complete, dormant non-dividing cells must be permitted to grow by interrupting treatment.

Methods of estimation in blood and body fluids

Very consistent results are obtained by two micromethods of estimating penicillin in blood serum and other body fluids. Fleming¹ describes first the preparation of slide cells, each

divided into 6 compartments holding 50 cubic millimetres, which allows a complete titration to be done in one set. One cubic centimetre of group O blood, which has had the leucocytes removed or inactivated, is inoculated with a large loopful of a 24 hour culture of a streptococcus known to produce a powerful haemolysin. Serial dilutions of the patient's serum are made with 25 cubic millimetre volume of physiological saline, and are mixed with equal volumes of the infected blood and run into the slide cells. These are carefully sealed, incubated overnight at 37° C. and examined horizontally by transmitted light. In the cells where streptococci grow freely, the blood is completely haemolysed, but it is unchanged in the cells containing a bacteriostatic concentration of penicillin. Alternatively, capillary tubes of about 0.8 millimetre bore and 3 inches in length are used as cultural vessels. Blood is infected with 5 cubic millimetres per cubic centimetre of a 24 hour broth culture of the test haemolytic streptococcus. Serial dilutions, of 25 cubic millimetre volume each, are made, and are mixed with 5 cubic millimetres of the infected blood (diluted with an equal volume of saline). Each drop is touched by the end of a capillary tube. The tube ends are sealed after the fluid in each has run to about the centre. The tubes are stuck in Plasticine on a slide and are incubated horizontally overnight, and are set upright for an hour before the result is read. Unhaemolysed corpuscles settle to the bottom of the tubes giving a clear end point. The size of the capillary tubes can readily be adjusted to allow testing when only minute quantities of fluid are obtainable from the patient.

Effect on blood coagulation

When patients are given penicillin intravenously, thrombosis is liable to develop. In order to measure this phenomenon by determinations of clotting and of bleeding time, Moldavsky and his colleagues gave penicillin to 20 patients both orally and intramuscularly. The concentration in the blood, and simultaneously the clotting time, bleeding time and prothrombin time, were measured. Determinations were made before penicillin was given and at 15-minute and 30 minute intervals afterwards. Food and water were withheld in order to maintain uniform conditions. A group of controls was also observed. The clotting time did not change in the control group but fell sharply when oral or intramuscular penicillin was given. As the concentration of penicillin in the blood rose the clotting time fell and persisted at a depressed level even after penicillin had entirely disappeared from the blood. The bleeding time remained constant in the control group and fell after penicillin administration. The change was not marked and seemed to be transient. The prothrombin time did not show any characteristic unidirectional change. The clot was also changed becoming non retractile.

Site of injection and its effect on potency

Herwick, Welch, Putnam and Gamboa describe studies on the correlation between the purity—which is also a measure of the potency—of commercial sodium penicillin and the irritative symptoms occurring after its intramuscular injection. Two hundred and thirty patients were treated with sodium penicillin from 17 different manufacturers. Preliminary investigation on 100 patients showed no correlation between vesiculation in man or oedema and haemorrhage in rabbits and pain on intramuscular injection in man. Although 6,000 units or more of certain preparations of penicillin which, injected intradermally, produced oedema and haemorrhage in rabbits, would nearly always cause pain on intramuscular injection in human patients, the converse did not hold. In another 100 cases penicillin of varying potencies, from several manufacturers, was tested and controlled by injection of 5 cubic centimetres of isotonic sodium chloride solution on the opposite side of the body, using buttocks, or triceps or deltoid muscles. Although this investigation showed that penicillin caused more pain on intramuscular injection than did isotonic solution of sodium chloride, that injection into the buttocks caused less pain than did injection into the triceps or deltoid muscles and that pain was in inverse proportion to potency as measured by light transmission, the data could not be statistically reviewed. A further 30 patients were therefore injected each with 25,000 units of sodium penicillin dissolved in isotonic solution of sodium chloride in a concentration of 5,000 units per cubic centimetre. Statistical analysis, by balanced incomplete block type of experimental design, confirmed the significant factors to be (1) the potency of the penicillin and (2) the site of injection.

Experiments with regard to potency

It is known that penicillin exerts a bacteriostatic effect on *Neisseria intracellularis* and on other Gram negative organisms, but Hobby maintains that it is possible to demonstrate a similar action on *Neisseria gonorrhoea*, and on other Gram negative organisms such as *Eberthella typhosa*, *Shigella paradysenteriae*, *Brucella abortus* and *Alebsiella pneumoniae*. The effect is enhanced by the use of penicillin of great potency. The antibacterial action was demonstrated *in vitro* with penicillin produced by *Penicillium notatum* or *Penicillium chrysogenum*. In the preliminary experiments the serial dilution method was employed and a stock strain of *E. typhosa* served as the test organism. The potency of the various preparations of penicillin ranged from 35,000 to 49,000 Oxford units per cubic centimetre. All the crude liquors showed some degree of bacteriostatic activity and the partially purified fractions inhibited the growth of *E. typhosa* in dilutions from 1 in 400 to 1 in 32,000. In the subsequent experiments it was found that the crystalline sodium penicillin was 64 times more potent against *Staphylococcus aureus* than against *E. typhosa*. The Gram negative organisms showed varying degrees of susceptibility but *Escherichia coli* and *Pseudomonas aeruginosa* were completely resistant. Further investigations may result in the discovery of a form of penicillin which has a more powerful action.

Optimum methods of administration

Fleming and his colleagues have estimated the concentration of penicillin in the blood serum of patients receiving the drug in various doses. A series of observations were made at intervals after the injections had been given. In each instance a regular curve was obtained, which suggests that the test is reasonably accurate. The curves showed that penicillin is very rapidly absorbed after intramuscular or subcutaneous injections. The rate of disappearance from the blood is not markedly different whether the injection is given intramuscularly or intravenously. Penicillin, injected intramuscularly, disappears from the blood 3 hours after a dose of 15,000 units, but the time of disappearance is increased to 6 hours after an injection of 100,000 units. The smaller doses are, however, more economical. For example, a continuous bacteriostatic power can be maintained in the blood for 12 hours by means of 6 doses of 15,000 units given every 2 hours.

Administration with gastric antacids

Penicillin if given by mouth is reported to be destroyed by the gastric juice and Charney, Alburn and Bernhart have conducted experiments to discover whether the administration of gastric antacids would cause improved absorption. It was found that only 3 per cent of a diluted oral dose of penicillin, given 2 hours after breakfast, was recovered in the urine. When given in conjunction with 5 grammes of trisodium citrate an average of 18 per cent was recovered in 21 cases, and 70 per cent of the amount recovered was excreted in the first 2 hours. Similar results were obtained when other antacids were used. The authors also investigated the effect of other factors on the absorption of penicillin. Urine passed at 2-hourly intervals over a period of 6-8 hours after dosage, was collected and the total amount of penicillin excreted was calculated. It was found that excretion was greater if penicillin was given either alone or with an antacid after an overnight fast than when it was given 2 hours after food, this result probably being due to lowered gastric acidity in the fasting subject. The addition of 1.4-7 grammes of trisodium citrate caused 100 per cent increase in urinary excretion compared with the amount excreted when penicillin was given alone 2 hours after breakfast. Large individual variations occurred in the total urinary penicillin excretion.

Penicillin therapy compared with penicillium therapy

Kenyon and his colleagues point out that there are distinct differences between penicillin therapy and penicillium therapy. In the former the sodium or calcium salt of penicillin A is used. This is extracted from the filtrate on which the mould of *Penicillium notatum* Fleming is grown. It does not contain the living hyphae or penicillin B, C and D. In penicillium therapy, the whole filtrate is used, containing all the known metabolites of the growth of *P. notatum*, living hyphae and possibly other unknown metabolites as well. Much research has been necessary in order to render the filtrates non-toxic, sterile and of standard adequate potency, and preparations answering these requirements, known as Vivicillin and Hypholin, are in clinical use. Certain specific factors are known to be produced by bacterial organisms—for example by *Staphylococcus aureus* in deep cultures—for which the authors suggest the name, antipenicilliums, since they inhibit the antibiotic activity of the penicilliums. Methods are described by which penicillium antibiotic preparations with an activity equivalent to many thousand Oxford units per cubic centimetre have been obtained which counteract *in vitro* the bacterial antipenicilliums and other factors which inactivate the antibiotics. It is claimed that these preparations compare favourably in clinical application and potency with pure extracted penicillin A, show specific activity in cases in which penicillin is inactive and can be made available in large quantities and at low cost. Hypholin, the most recent development of this type of preparation, is fluid, diffuses readily in wounds and is not inhibited by germs or pus in infected wounds. Intramuscular injection appears to cause clinical improvement in a wide range of systemic infections and examples are given of its action in acute carbuncle, acute cerebrospinal meningitis, primary pneumonia and acute *Streptococcus viridans* septicæmia. In a limited experience, its use by the intravenous route is said to be harmless.

Privine

Studies on dogs

Graver, Chase and Yonkman present the results of pharmacological studies on anesthetized dogs with 2-naphthyl-(1'-methyl-imidazoline hydrochloride, known also as privine or naphthazoline. This report refers particularly to the vascular and respiratory reactions produced. Privine elevates the blood pressure in doses of the same order of magnitude as are required for epinephrine (adrenaline) but to a less extent. The action of privine is partially inhibited but is not reversed by yohimbine hydrochloride and ethyl yohimbine. It is not potentiated by cocaine. It exhibits tachyphylaxis, but rarely and only to a slight degree. When administered gastrically or rectally in large doses privine reveals no systemic evidences of absorption. Relatively large doses administered nasally, intraperitoneally, or within the ileum, exhibit minimal systemic changes. It appears to be synergistic with sodium pentobarbital (soluble pentobarbitone) in its depressant action on respiration but no evidence of such depression in dogs anesthetized with ether or urethane could be elicited. The authors suggest that privine acts not only on sympathetic endings but on smooth muscle directly; this would explain the ability of an augmented dose to act myotropically beyond endings paralysed by yohimbine. It would also explain its failure to relax bronchioles in an isolated guinea-pig lung, as noted by another observer. The tendency, however, for repeated large doses to exhaust the animal's capacity to respond without causing very significant changes in the kymographic respiratory

lauryl alcohol. In one series of experiments the drug, both alone and with the detergent, was applied by means of a celluloid funnel to the eyes of rabbits *in vivo* and *in vitro*, and also to eyes with denuded corneas. In another series of experiments drops were instilled into the conjunctival sacs of rabbits. In the final experiment, the effect of the addition of Duponal on the penetration of the drug into excised portions of the eye was studied. It was found that the addition of Duponal caused a marked increase in the amount of the drug to reach all tissues of the eye with no significant difference *in vivo* and *in vitro* except in the conjunctiva. Denudation of the cornea caused greatly increased penetration of the drug and the addition of the detergent did not increase the permeability of this denuded cornea. Experiments on the individual tissues showed that Duponal increased the penetration of sodium sulphacetamide in the intact cornea but not in the denuded cornea or sclera. The authors concluded from the above experiments that the epithelium of the cornea acts as a barrier to the penetration of the drug into the cornea, and that the wetting agent by overcoming the barrier may increase the penetration.

Thiouracil

Estimation in urine

Anderson describes the estimation of thiouracil in urine by Grote's reagent which, originally used for thiourea, was found to be suitable for thiouracil. The reagent is not stable, deteriorating after 10 days, therefore standards must be prepared for each batch of estimations. It gives a blue colour with compounds containing the group C=S, as well as with thiouracil and thiourea, but a number of pathological urines tested with it gave no trace of blue or of green colour. Weighed amounts of thiouracil added to urine were recovered with an error of not more than 5 per cent. The excretion of thiouracil was observed in 2 patients who were under treatment for hyperthyroidism, the dosage given being 1-1.2 grammes daily. Only a small amount was excreted at first, but by the end of a week 60-70 per cent of the daily dose appeared in the urine, and the excretion remained thereafter at that level. It was assumed that the compound which gave the reaction was unchanged thiouracil. It is not excreted as thiourea since the urine of one of the patients, when tested for this, was found to be negative.

Absorption by various tissues

Williams, Kay and Jandorf describe experiments with thiouracil on rats and on human beings. The gastro-intestinal tract rapidly absorbs the drug and none is eliminated in the faeces. Colon bacilli do not destroy the compound but staphylococci and streptococci account for the destruction of amounts varying from 35 to 50 per cent. The total amount of thiouracil excreted in the urine is about one-third of the quantity ingested and one-half of the amount injected intravenously. One subject who had received 1.2 grammes daily for 3 days had a blood level of 1.6 milligrams per 100 cubic centimetres 24 hours after discontinuation of the drug. On the next day no thiouracil was present in the blood and none was detected in the urine within 4 days of cessation of treatment. The total quantity excreted in the urine after discontinuation of the drug was equal to that previously excreted daily. With doses ranging from 0.2 to 1.2 grammes daily the concentration of the drug in the blood varied from 0.8 to 6.4 milligrams and the daily excretion in the urine varied from 16 to 618 milligrams. In the case of the blood most of the drug was found in the cells. The concentration was greater in the leucocytes than in the erythrocytes but the latter contained a larger total amount. Whole blood contained more thiouracil than did cerebrospinal fluid, oedema or pericardial fluid but the proportion of the drug was essentially the same as that in pleural and ascitic fluids. Milk, however, contained three times as much as did the blood. Thiouracil was present in almost all the tissues but the greatest concentration was found in the bone marrow, the hypophysis, and the thyroid and suprarenal glands. Adenomas of the thyroid gland possessed a much greater proportion of the drug than did the normal thyroid gland.

Tyrothricin

Its activities against Plasmodium gallinaceum

Taliaferro, Coulston and Silverman describe experiments with tyrothricin, indicating that this antibiotic substance shows a marked curative and suppressive antimalarial activity against sporozoite-induced and blood-induced infections with *Plasmodium gallinaceum* when it is administered intravenously to chickens in a 9.5 per cent alcoholic dilution. When given in dosage of 0.2 milligram approximately daily for 9-15 days, from the onset of infection, tyrothricin lengthened the incubation period of blood-induced infections; it lowered the peak of the acute infection and usually prevented fatal, but not slight, relapses in both sporozoite-induced and blood-induced infections. From 2 to 6 doses of 0.3 or 0.4 milligram also suppressed the acute rise of blood-induced infections if the treatment was initiated when peripheral parasites first appeared, but did not prevent fatal relapses; if initiated after the parasites exceeded 7,500 per 10,000 erythrocytes, the treatment became progressively less effective until it was wholly useless. Tyrothricin was ineffective when given intravenously in distilled water or intraperitoneally in 9.5 per cent alcohol or in distilled water, or orally as a powder. The drug was shown to have a quinine equivalent of approximately 4, but its effective dose was nearer the toxic level than was that of quinine. Tyrothricin's action was mainly parasiticidal, especially on the extracellular merozoites produced at segmentation, whereas quinine predominantly affects the parasites' reproduction. Tyrothricin was more effective than was quinine in inhibiting the oxygen consumption of erythrocytes parasitized with *P. gallinaceum*. A few tests with the gramicidin component of tyrothricin indicated that 0.4 milligram adminis-

tered as for tyrothricin markedly suppressed blood induced infections with *P. gallinaceum*. The normal course of *P. gallinaceum* in chickens, as previously described, was confirmed. Exo-erythrocytic forms were found, sometimes associated with fatal relapses occurring about 3 weeks after blood induced infections. Segmenters of this parasite generally formed 12-32 merozoites with a mean of 17-24, during the acute rise of the infection.

PHARMACOLOGICAL EFFECTS ON DRUG GROUPS

Antibiotics

Produced by moulds

Pinschmidt and Levy describe a simple method for the routine search for antibiotic substances produced by moulds. A series of tubes, each containing 10 cubic centimetres of sterile nutrient broth at a hydrogen ion concentration of $6.8 \pm$, is inoculated with 0.1 cubic centimetre of a 24-hour broth culture of *Staphylococcus aureus* (Reddish strain). A second series is similarly inoculated with 0.1 cubic centimetre of a 24-hour broth culture of *Eberthella typhosa* (Hopkins's strain). A small piece of the surface growth, or a loopful of spore suspension of each mould to be tested, is floated on the surface of one tube of broth containing the *Staph. aureus* and one containing the *E. typhosa*. The tubes are incubated at room temperature for 10 days or until a heavy surface growth of the mould is obtained. Daily observations are made for clearance of the turbid bacterial substrate. The results obtained by this method are not dependent upon occlusion of the bacterial culture surface by the moulds or upon the hydrogen ion concentration produced by the moulds, and appear to be a direct measure of the production of antibiotic substances. In almost every tube in which clearance occurred in these experiments a clear discrete ring formed first directly beneath the mould mycelium.

Experiments on tetanus toxin

Since the therapeutic efficiency of penicillin has been established, interest has been renewed in the properties of antibiotic substances in the reduction of the toxicity of bacterial exotoxins. Neter describes the experimental effects of penicillin, clavacin and streptomycin upon tetanus toxin when injected into mice with suitable controls. In 1902 it was reported that pyocyanase detoxifies diphtheria toxin and it was later stated that it also detoxifies tetanus toxin. There is no evidence of detoxification of tetanus toxin when it is mixed with 500 Oxford units of sodium penicillin. Incubation for 48 hours at 37°C of a mixture containing 1,000 Oxford units results in a slight reduction of toxicity of the tetanus toxin. Tetanus toxin in a dilution of 1 in 10,000 is mixed with 0.2 milligram and 0.02 milligram of clavacin. Tetanus toxin unmixed causes signs of tetanus in 18 hours, mixed with 0.2 milligram of clavacin signs of tetanus appear in 48-72 hours, mixed with 0.02 milligram of clavacin it shows signs of tetanus after 24-30 hours. Clavacin therefore has upon tetanus toxin a detoxifying effect which is more easily seen when larger amounts are used. Streptomycin in amounts of 10 milligrams fails to prevent the toxic effects of tetanus toxin. As yet little is known of the effects of antibiotic substances upon bacterial toxins. Of those so far tested clavacin and pyocyanase are the only ones that have the property of detoxifying tetanus toxin but it is likely that others may also possess this power.

Barbiturates

Electroencephalographic reactions in psychoneurosis

Brazier and Finesinger describe the changes in the electroencephalograms which resulted from the slow intravenous injection of barbiturates in patients with psychoneurosis. The drugs consisted of sodium Amytal, Pentothal sodium (soluble thiopentone) and sodium pentobarbital (soluble pentobarbitone). In each experiment 3 grains of one of these barbiturates were injected during a period of 4 minutes. The injection sufficed to produce a high-voltage fast activity in the encephalogram. The effect was observed first in the frontal leads, then in the parietal leads and finally in the occipital leads. When the patient was allowed to recover from the effect of the drug, the regression was in the opposite direction. The voltages of the most pronounced effect in the regions of the cortex which are of most recent ontogenetic and phylogenetic development. With increased dosage a second effect was seen: the frequency slowed until δ -waves of 3-4 per second developed. Three patients were given sodium amyltal by mouth in doses of 9 grains. The electroencephalogram of one patient did not show any effect. The second patient went to sleep and the electroencephalogram showed normal sleep waves. In the third patient's record all the effects were observed with intravenous injection, but there was a longer latent period. There are obviously wide individual differences in the reaction to the drug. A normal sleep pattern develops in a patient who is sleeping deeply under the influence of a barbiturate. When the patient is roused from drugged sleep, the activity typical of the drug. It is believed that the barbiturates modify the frequencies of brain waves by inhibiting the activity of the dehydrogenase systems of cellular activity.

Curare

Effect of curare and similar substances on the central nervous system

Pick and Unna describe experiments demonstrating that *d* tubocurarine chloride, dihydro- β -erythroidine hydrochloride, quinine ethochloride, nicotine base and thiamine hydrochloride not only block the myoneural junction but also diminish and, in large doses, suppress, the

frequency and amplitude of the potentials as observed in electroencephalograms of pithed frogs. The doses of curare and erythroidine which effectively decreased the brain's electrical activity were slightly larger than were those needed to block transmission at the myoneural junctions, and $\frac{1}{10}$ - $\frac{1}{20}$ of the dose of thiamine hydrochloride affecting these junctions suppressed the electrical potentials of the brain; even these quantities are greater than the amount of thiamine found to be essential for adequate carbohydrate metabolism. Another difference noticed in the effects produced by these substances (except quinine ethochloride) upon the electroencephalogram and the myoneural junctions, respectively, was the much longer duration of the inhibition of the brain's electrical activity, which persisted after restoration of function of the myoneural junctions. The authors suggest that the electroencephalogram variations observed were due to a blocking of the synapses of the central nervous system, as indicated by Libet and Gerard's previous experiments with nicotine. Sodium cyanide and monoiodoacetic acid inhibited and almost completely abolished the electrical activity of the frog's brain. Prostigmin alone depressed brain potentials and counteracted the effects upon the neuromuscular functions of the curare-like substances investigated but did not counteract their effects upon the central nervous system.

Sulphonamides

Summary of recent researches

Hawking summarizes recent work on the pharmacology of the sulphonamides. Absorption occurs chiefly in the small intestine but probably to some extent through the stomach wall. In dogs, about 4 hours after an oral dose, the substance is distributed approximately evenly through all the tissues except bone and fat. Sulphonamides pass through the placenta and prolonged dosage is injurious to the fetus. The amount appearing in mother's milk is not toxic or of therapeutic use to the infant. Part of the sulphonamide in plasma is bound to the proteins, principally the plasma albumins, a combination which probably explains the different distribution between plasma and erythrocytes and between blood and cerebrospinal fluid, and plays some part in the production of sensitization phenomena. Much of the sulphonamide introduced into the body is conjugated to form acetyl derivatives which are therapeutically inert. Acetylation occurs mostly in the liver. Of the newer sulphonamides, sulphamerazine (sulphamethylpyrimidine) is similar in activity to sulphadiazine and sulphadimethylpyrimidine (sulphamezathine) but it produces a more persistently high concentration in the blood. Sulphapyrazine is incompletely absorbed and would therefore appear to be indicated for use in bacillary dysentery, for which sulphaguanidine and succinylsulphathiazole have already been used. Promanide (promin) restrains the development of experimental tuberculosis in guineapigs but in man it produces toxic symptoms, chiefly haemolytic, which balance its benefits. The action of Promizole is similar but is less toxic. Marfanil differs from all other sulphonamides in that the amino group is separated from the benzene ring by a methyl group. It is much more active against anaerobic infections and has been used extensively in the German army as a Marfanil-Prontosil rubrum powder for local application to wounds. The solubility of the various sulphonamide compounds varies considerably. Relatively highly soluble are sulphanilamide, sulphaguanidine, sulphacetamide, sulphadimethylpyrimidine and acetylsulphanilamide. The least soluble are sulphapyridine, sulphadiazine and their acetyl derivatives and acetylsulphathiazole.

Bactericidal effects

Colebrook and Cawston describe experiments in which specimens of broth, with and without an added sulphonamide, were implanted with a diluted culture of haemolytic streptococci. Viable counts were made by explanting an aliquot part of each tube in melted blood agar with *p*-aminobenzoic acid, immediately and after incubation for 6 hours. The remainder of the infected broth was explanted in a similar way after further incubation for 18 hours. Four strains of streptococci were used and all were killed with the exception of a single colony which grew from the sulphonamide broth after 24 hours. The results were obtained with sulphanilamide, sulphapyridine, and sulphathiazole. These substances had evidently exerted a bactericidal as well as a bacteriostatic effect. Other experiments indicated that serum containing sulphonamides will often reduce the viable count within 24 hours from several thousand to less than a hundred. Killing of that order by all the body fluids may play an important part in suppressing an incipient infection by susceptible organisms. Haemolytic streptococci may survive for months without added fresh nutriment. This fact suggests that interference with the organism's metabolism is not enough to account for the rapid change to the non-viable state under experimental conditions.

Renal complications analysed

Prien discusses the mechanisms of renal complications in sulphonamide therapy. The usual mechanism is the obstruction of the urinary channels by insoluble concretions composed principally of acetyl derivatives of the drugs. Less often anuria and uraemia is caused by toxic injury of the tubules, independent of concretions, when the only lesion in the urinary tract may be a widely disseminated focal necrosis of the tubules. Such a condition was found in 2 cases reported on here of sulphathiazole anuria and uraemia. In the first case, that of a man with pneumonia, no obstructing concretions were found in the ureters or kidney pelves by cystoscopy or pyelography. Renal decapsulation was done and cortical biopsies were taken. On examination after death both kidneys were swollen: neither crystals nor concretions were found but there was widespread focal degeneration of the tubules. In the second case, that of a

woman with septic pharyngitis, the patient recovered after decapsulation of the left kidney. In this case also there were scattered areas of necrosis but no crystalline material or pus. In order to prevent the possible loss of crystals by solution, frozen sections were cut and transferred by a frozen microtome knife directly on to frozen slides and were examined in a drop of mineral oil with a polarizing microscope. Low urinary output is the most important factor in causing renal complications and the development of obstructing concretions depends upon the hydrodynamics of the urinary tract and the affinity of crystals for each other. Sulphonamide crystals form first in the convoluted tubules, and sedimentation occurs in the terminal portions of the collecting tubules and in the renal calyx. Proximity of crystals results in aggregation and in the formation of concretions which obstruct the terminal portions of the collecting tubes. The process continues up the collecting tubes in a retrograde manner. Calyceal concretions behave as do ordinary urinary calculi.

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infection are insidious in onset, relatively frequent and often serious. Ten patients were without tonsils and had no complications. Among 44 patients with tonsils, there were 4 with peritonsillar abscess, 1 with pneumonia, 1 with rheumatic fever and 5 with scarlet fever, of whom 1 of the last-mentioned category had acute sinusitis and pneumonia. In these cases there was only a slight increase or no increase in the leucocyte count. Seventeen cases were designated control patients, 11 of them receiving sulphadiazine and 6 no specific treatment. Peritonsillar abscess developed in one patient in each group, otherwise there were no clinical relapses. Throat cultures in all but 3 of these 17 cases were positive 7–18 days after the onset. Penicillin was used in 9 cases in doses of 15,000 units given intramuscularly every 4 hours for 3–4 days. There was a striking immediate clinical response. In 24 hours the patients were free from symptoms and had normal temperatures; rapid retrogression of pharyngeal involvement was observed, and in 48 hours negative cultures were the rule. In 4 of these cases, 24 hours after administration of penicillin had been stopped, haemolytic streptococci again appeared on culture and in 48 hours clinical relapse occurred. In the remaining 5 there was no clinical relapse and cultures were negative. It is believed that the rapid initial response to penicillin therapy interferes with the normal development of immunity. A further 9 patients were given a 24-hour course, 6 receiving 150,000 units, and 3 receiving 100,000 units with routine sulphadiazine therapy. Haemolytic streptococci regularly returned in all but 1 case. Penicillin therapy was extended to 6 days, 15,000 units being given every 4 hours with very favourable results and neither clinical relapse nor return of haemolytic streptococci occurred.

Endemic exudative pharyngitis

Bacteriological discussion.—Research into the aetiology and clinical characteristics of endemic exudative pharyngitis and tonsillitis was carried out at a regional hospital in North Carolina by members of a Commission on Acute Respiratory Diseases and their associates and helpers. Twenty-five per cent of the 116 cases investigated displayed β -haemolytic streptococci on culture and increased streptococci antibodies in sera during convalescence. In another 25 per cent streptococci were grown but rise in antibodies was absent on repeated culture. Well defined clinical differences were noted between the streptococci plus antibody cases and the others; symptoms appeared more rapidly and affected a greater proportion of the first group of patients than they did in those without streptococci or in those with streptococci but without increased antibodies. Sore throat, present in nearly all cases, occurred earlier—within 24 hours—in the antibody group. Cough and hoarseness, present in about half the number of cases, occurred much more often when streptococci were absent. Injection of the tonsils, soft palate and pharynx, oedema of the uvula and exudate on the tonsils occurred with equal frequency in all groups but diffuse injection of these tissues was twice as often seen in the streptococci plus antibody group. Increased antibodies developed more frequently in patients who displayed large amounts of exudate and it was deduced that extensive exudate indicated presence of large numbers of streptococci. It was also noted that these patients showed distinct leucocytosis. It is contended that in most patients who lack antibodies, streptococci are not the primary cause of exudate and “may have no more relation to the infection than any of the other bacteria normally present in the throat”.

Commission on Acute Respiratory Diseases (1944) *J. Amer. med. Ass.*, 125, 1163.

Plummer, N., Duerschner, Dorothy R., Warren, H. D., Rogliano, F. T., and Sloan, R. A. (1945) *J. Amer. med. Ass.*, 127, 369.

PHLEBOTOMUS FEVER

See also B.E.M.P., Vol. IX, p. 583; and Cumulative Supplement, Key No. 1258.

Aetiology

Vector

Notes on sandfly fever and the phlebotomus papatasi.—Sabin, Philip and Paul have been investigating sandfly fever with the help of human volunteers. They stress the military importance of this 3-day fever which closely resembles influenza except that upper respiratory tract symptoms are absent. It has a widespread distribution in tropical and subtropical lowlands during hot dry weather, and is caused by a small-sized filter-passing virus. Serum obtained from spontaneous cases regularly reproduced the disease in human volunteers, 95 per cent of whom were found to be susceptible, irrespective of sex and colour. In the experimentally produced disease the virus was found in the blood for 24 hours before and after the onset of the infection, and disappeared thereafter. Attempts to transmit the disease to lower animals failed and it did not appear to be possible to propagate the virus in chick embryo cultures. Controlled tests with mosquitoes and human fleas showed they were unable to transmit the disease, and previous work had exonerated the bedbug. The vector, *Phlebotomus papatasi*, is a midge too small to be kept out by the ordinary mosquito bar. The bite is painful, and sensitivity to future bites is very likely to develop. The flight range is short, but the disturbances of ground incident to the establishment of military installations can provide good breeding grounds for it. The eggs develop into adult flies in from 4½ to 6 weeks, but the life of the latter is believed to be short: 2–3 weeks in the laboratory. The disease is maintained in nature by passage from man to man through the medium of *Phlebotomus papatasi*. As the virus disappears so rapidly from the blood of human beings, it is not clear what the reservoir of the virus is during the late autumn and winter months when the flies are absent. Experiments indicated that the virus is not passed on from generation to genera-

tion in all infected flies, previous work suggests that this transmission may occur occasionally and perhaps often enough to carry the virus over from one season to another

Treatment

Dimethyl phthalate

Philip, Paul and Sabin report on dimethyl phthalate as a repellent in control of phlebotomus (sandfly) fever. They conducted their investigations during 5 weeks at the height of an epidemic of sandfly fever, on soldiers in barracks near Cairo. The men slept in wooden buildings or tents, surrounded by urban buildings, trees and vegetation, and contact with natives and animals could have been fairly close. This environment is considered to be significant in view of the very rare incidence of sandfly fever which was noted even during epidemic seasons in an isolated desert camp within a few miles of the barracks. Two fluid ounces of the repellent were issued to each of a group of men with instructions that it should be lightly applied at sundown and again before sleep to the parts of the body exposed during the night. Individuals of another group of almost the same size were instructed to use a control, consisting of distilled water, in the same way. The men were given the impression that they were all using the same lotion. In the group which received the repellent, it was found that only 12 per cent considered it to be ineffective against sandfly bites, and the 2 men in this group in whom the disease developed admitted that they had failed to apply the repellent for several consecutive nights. Of the control group 42 per cent believed their lotion to be ineffective against the bites, and in 10.8 per cent the disease developed. Tanglefoot fly paper traps were used to estimate the sandfly population, and a distinct correlation was found between the prevalence of the flies and the distribution of cases.

Philip, C. B., Paul, J. R., and Sabin, A. B. (1944) *War Med.*, 6, 27

Sabin, A. B., Philip, C. B., and Paul, J. R. (1944) *J. Amer. med. Ass.*, 125, 603

PHYSICAL MEDICINE

Hypothermy

Hypothermy compared with hypothermia

In eye diseases—From earliest times heat and cold have been used as therapeutic agents and Celsus in A.D. 25 discussed the relative merits of the two methods. Rodin reviews their application to diseases of the eye, pointing out that heat is a vasodilator, producing increased hyperaemia and accelerating metabolism and leucocytosis. Cold is a constrictor, allaying pain and promoting healing by the production of local anaemia. The decision to use heat or cold in diseases of the eye may often depend upon the patient's comfort and reaction to one or the other form of therapy but, in general, Rodin advises heat for most inflammatory conditions, particularly those of the anterior segment of the eyeball. Heat, however, also promotes recovery in conditions unidentified with pain, such as turbidity of the vitreous, intra-ocular haemorrhage and choroidal disease. Cold is applicable in lesions produced by physical or chemical trauma, early conjunctivitis, blepharorrhoea and acute trachoma and in postoperative care. Rodin favours the local application of heat and cold by a method first described by Parsons and used at Moorfields Eye Hospital, London. Cottonwool is tied into the bowl of a wooden spoon which is then dipped into boiling water or cold water, as the case may be, before it is applied to the closed lid.

Hypothermy

Methods of supercooling the skin

Clinical picture—Lewis describes a reliable method of whealing the skin by supercooling. The cutaneous surface of the front of the forearm is cooled by means of a bar of copper. One end of the bar is immersed in acetone cooled by adding carbon dioxide snow, and the other end is applied to the skin. The temperature is read from a thermal junction attached to the surface of the metal. Freezing of the skin is avoided by keeping the surface of the copper free of frost. In most cases the skin can be supercooled to -20°C or -25°C for periods of time varying from 10 to 120 seconds. Full whealing occurs within 2–5 minutes and subsides in about an hour. Redness of the skin rarely lasts for more than a few hours. It is considered that the injury to the skin begins at the temperature of 18°C . There is a slow increase in intensity as zero is approached but the intensity rises abruptly in the lower levels of supercooling. The skin excised after death can be supercooled as effectively as can live skin. In each case cooling can be effected so that the surface is at about the temperature of -21°C without the accompaniment of freezing. The acute results of supercooling must be distinguished from those of true frostbite. Although supercooling at -15°C for 10 minutes does not produce wheals yet whealing is produced by freezing the skin at the same temperature for 20–30 seconds. Furthermore, freezing produces certain additional effects which include persistent reddening and tenderness, pigmentation and desquamation. Both supercooling and freezing produce the triple response, but the delayed after-effects of freezing are much the more conspicuous and introduce reactions which are far less easily reversed or repaired.

Effect on heart rate

Experiments on rats—Crissmon discusses the effect of hypothermia in rats anaesthetized and then cooled by being placed on a copper tubing through which cold water was circulating. Their heart rates and arterial pressures were recorded and electrocardiograms were made during a period of steady reduction in body temperature measured rectally. It was found that reduction in the heart rate showed a uniform correlation with the fall in body temperature,

the relationship being linear between 15 and 35° C., with more variation above and below these levels. The arterial pressure due to vasoconstriction of the peripheral vessels and to shivering rose to 29° C. It then fell slightly to 21° C., below which the fall was precipitous. Below 20° C., when the heart rate was one-third of the normal, a linear relationship existed between the fall in arterial pressure and heart rate and it seems to be certain that the reduced cardiac output is ultimately responsible for peripheral circulatory failure in hypothermia. Electrocardiograms showed inversions of the P wave, followed at lower temperatures by sino-auricular block and shifting of the pace-maker. On further cooling complete auriculo-ventricular block resulted, which was corrected by administration of artificial respiration or by the slow rise of body temperature during recovery. The author found that respiratory failure did not occur until the body temperature fell to 15–21° C. As irreversible damage to the respiratory centre occurs in animals with less impairment of the circulation at almost normal temperatures, Crismon considers it to be unreasonable to attribute the respiratory failure in hypothermia entirely to the direct effect of cold on the respiratory centre.

Crismon, J. M. (1944) *Arch. intern. Med.*, 74, 235.

Lewis, T. (1944) *Clin. Sci.*, 5, 9.

Rodin, F. H. (1944) *Arch. Ophthal.*, N.Y., 32, 296.

PITUITARY GLAND DISEASES

See also B.E.M.P., Vol. IX, p. 611, and Cumulative Supplement, Key Nos. 1263–1268.

Cushing's syndrome

Aetiology

Effect of suprarenal cortical hormone.—Heinbecker reports clinical and experimental studies bearing on the pathogenesis of a syndrome described by Cushing in 1932. The characteristics were given as a painful adiposity of face, neck and trunk, kyphosis of the upper thoracic spine, hypertrichosis of face, neck and trunk in females, pre-adolescence in males, dusky plethoric appearance of the skin with purplish lineae atrophicae on abdomen and thighs, hypertension, variable backaches, abdominal pains and ultimately extensive weakness, dryness of the skin with acne, and susceptibility to skin infections. Other conditions sometimes found were hyperglycaemia, glycosuria, diminished sugar tolerance, polyphagia, polydipsia, osteoporosis, bronze pigmentation of skin, cutis marmorata and purpuric ecchymoses. Cushing considered the syndrome to be primarily due to a basophil adenoma of the hypophysis. Later it was established that basophil adenomata occur without Cushing's syndrome, and that the syndrome is found without basophil adenomata. No one pathological condition was consistently found, until in 1935 it was finally established that a constant condition was a peculiar hyalinization of the basophil cells of the hypophysis. It has been shown that a localized lesion involving the hypothalamic nuclei, especially the paraventricular nucleus, always produces adiposity. In 6 patients with Cushing's syndrome investigated by Heinbecker, the hypothalamus was studied in 5, and in these well marked hyalinization of basophil cells was found. In 4 cases there were changes in the hypothalamic nuclei, particularly the paraventricular nuclei; in none was there a suprarenal tumour. In the fifth case a malignant suprarenal tumour was found, but no hypothalamic lesion. In the sixth case a suprarenal tumour was removed by operation, but the brain was not available for study. In dogs, a hypothalamic lesion involving the para-optic and paraventricular nuclei was experimentally produced. Diabetes insipidus and obesity developed in the animals. Alterations were found in the thyroid, the pancreas and the gonads, but not in the suprarenal glands. It is concluded that many of the findings typical of Cushing's syndrome may be caused by the basophil degeneration, which is due either to a suprarenal tumour or to hypofunction of the paraventricular hypothalamic nuclei. It is suggested that increased action of the suprarenal cortical hormone may start the process.

Clinical picture

With associated post-mortem findings.—LeCompte reports a case of pituitary basophilism associated with a suprarenal tumour of uncertain histogenesis. The patient, a married woman of 31 years of age, gave a family history of mental instability. She was subject to attacks of renal colic and had passed stones from time to time. Obesity, abdominal striae and hirsuties were noted on her admission to hospital. Amenorrhoea was complete and the clitoris was enlarged. A high blood sugar level necessitated insulin treatment but attacks of hypoglycaemia ensued. Subsequently, all the characteristics of Cushing's syndrome were manifested, except polycythaemia. There was a masculine distribution of hair and acne was seen on the face and trunk. The face presented a moonlike cyanotic appearance and moderate exophthalmos. The blood pressure was raised and a state of mental apathy and confusion ensued. A right axillary abscess and a right pulmonary infarct with pleural effusion developed. Death occurred rather suddenly with a final temperature of 107° F. Post-mortem findings included osteoporosis, multiple healed fractures of the ribs, cardiac hypertrophy and arteriosclerosis of the kidneys. Hyaline changes were seen in the basophil cells of the hypophysis. There was a neoplasm of the right suprarenal gland but histochemical methods failed to determine whether the tumour was of cortical or of medullary origin. Iron haematoxylin and ponceau-fuchsin stains gave negative results. Assays of the neoplastic tissue were also negative, but there was an increase in urinary androgens. The tumour contained many necrotic cells and a variety of other cells arranged in sheets or cords around large sinusoidal blood vessels. A few cells

contained a fine yellow-brown pigment and it is possible that the tumour was a pheochromocytoma. It is suggested that in cases of this type more information may be obtained by histochemical methods and assays for adrenaline and steroid hormones than by histological examination.

Heinbecker, P (1944) *Medicine, Baltimore*, 23, 225

LeCompte, P M (1944) *Amer J Path*, 20, 689

PLACENTA: DEVELOPMENT AND DISEASES

See also B E M P Vol IX, p 641

Functions

Glycogenic

Examination of placental tissues—Dempsey and Wislocki discuss the value of certain histochemical reactions in the examination of placental tissue for lipids, glycogen and iron. The lipids occur almost entirely as droplets in the syncytial trophoblast. These droplets give positive reactions for steroid hormones. Fresh villi were examined with the polarizing microscope. The birefringent lipid droplets were considerably smaller in the older placenta than in the younger specimens. Tests for fluorescence showed the presence of a greenish light in the outermost layer of the villi, it is noteworthy that the ovarian steroids give rise to this fluorescence. In some cases negative results were obtained from the Liebermann-Burchardt (strong sulphuric acid) test for sterol substances. A faint reddish colour developed immediately after the application of the acid to preparations fixed in formalin, and gradually darkened to a greenish brown. The Schiff test was used because the reaction test discloses certain fat-soluble materials in organs which have an active sterol metabolism. An immediate reaction occurred, as indicated by the development of a violet colour in the outer layer of the villi. Heavy deposits of glycogen were detected in the cytotrophoblastic cell columns and shell, in the trophoblastic cell islands and in the maternal decidua of the first half of pregnancy. It is significant that these tissues are characterized by a relative or complete avascularity and by deficient mechanisms for aerobic oxidation. Apparently, an intense anaerobic mechanism requires a large accumulation of glycogen for the purpose of maintaining the fermentative processes. Considerable quantities of iron were found in the syncytial and cytotrophoblastic elements of young placentae. The amount was greatly reduced in the later stages of pregnancy. It is concluded that the perinuclear deposits of iron are associated with the cytochrome system. The deposits scattered in the cytoplasm may represent iron of passage.

Dempsey, E W, and Wislocki, G B (1944) *Endocrinology*, 35, 409

PLEURISY

See also B E M P, Vol IX, p 699, and Cumulative Supplement, Key No 1277

Treatment

Treatment of effusions

Aspiration—Ellis reviews the significance of pleural effusion. History and any additional signs are aetiologically important. Transudates may accompany heart or kidney disease or ovarian disease occurring in Meigs's syndrome. Dry and serofibrinous pleuritis often occur in pulmonary tuberculosis less commonly in lobar and bronchopneumonias, pulmonary infarcts or intrathoracic new growths. Empyema, when secondary to pneumonia, is evidence of massive or virulent infection. Tuberculosis, septic infarcts and neoplasms, bronchiectasis, abscess and gangrene are other causes of pleural effusion. Haemorrhagic effusions may accompany intrathoracic neoplasms. Haemothorax results from injury to or disease of pulmonary vessels, mediastinum or chest wall. When a penetrating wound causes a haemopneumothorax, aspiration in order to allow the lung to re-expand and prophylactic intrapleural injection of penicillin will usually give good results. Chylous effusions, due to injury to the thoracic duct, are rare. X ray examination and the Casoni reaction assist diagnosis of hydatid disease affecting the pleura. One specimen of pleural fluid should be for cytological, another for bacteriological, examination. Contaminating saprophytes cause offensive empyemas. In effusion, the stage of the disease, the associated pulmonary condition and the patient's state are factors requiring consideration. Active and acute pulmonary disease usually contra indicates removal of fluid, and thus the lung is kept at rest. After aspiration of a small sample, clear fluid should be left unless it is sufficient to cause respiratory and cardiac distress, in such a case 1 or 2 pints should be removed. Otherwise, if there is no apparent absorption 14 days after its discovery, fluid should be aspirated in order to prevent possible permanent lung collapse. The possibility of latent pulmonary tuberculosis should be investigated. Immediate aspiration of an empyema relieves toxæmia. Closed drainage through a self retaining catheter is practicable until rib resection and institution of open drainage can be tolerated.

Ellis, R (1945) *Med Pr*, 213, 122

PNEUMOCONIOSIS

See also B E M P, Vol IX, p 708, and Cumulative Supplement, Key No 1278

Aetiology

Forms of pneumoconiosis

Effect of graphite on the lungs—Dunner describes radiological appearances in 5 male patients who had been working with graphite for periods of from 17 to 34 years. The occupa-

tional disease caused by inhalation of pure graphite has not, apparently, been previously described in Great Britain although references by foreign authors are quoted in *Occupation and Health*, a publication of the International Labour Office, Geneva, 1930, Supplement 1939. The graphite was inhaled for several hours daily but there was no question of admixture with other harmful dust as is the case when graphite is quarried or is otherwise extracted as a mineral. In the cases described both symptoms and physical signs were slight compared with the amount of pathological changes displayed radiologically; these conformed to no particular type but varied in different cases and suggested individual susceptibility; of 2 patients, for example, who had been working for 18 and 17 years respectively with graphite, the former did not show any symptoms and only 2 small foci radiologically, whereas the films made of the latter displayed extensive lesions. The author contends that there should be close enquiry into the exact nature of the work of any patient who displays radiologically marked striation or fibrosis of the lungs, whether or not the cause is thought to be known, or when the x-ray appearances suggest tuberculosis although repeated sputum examination has failed to reveal tubercle bacilli. The 5 patients whose cases Dunner investigated all worked only with graphite and had not been employed on other work likely to have caused pneumoconiosis. The graphite concerned was said to be the pure substance; investigation of its physical and chemical properties had not been made, however, and it is therefore not known whether or not particles of graphite dust display the sharp edges considered to be necessary for production of lung disease. The 5 men are, so far, apparently free from tuberculosis. Repeated examination of sputum (if available) is urged in such cases. The author emphasizes that radiology does not usually aid diagnosis of superimposed tuberculosis.

Diagnosis

Differential diagnosis

Benign non-specific pneumoconiosis results from the inhalation of dusts which are neither toxic, allergenic nor pathogenic, and which never produce symptoms, disability, true nodulation in the lungs or a predisposition to tuberculosis. The condition has already been recorded in baryta miners in Italy (baritosis) and in electric welders (siderosis), and Pendergrass and Leopold now describe 4 cases in metal grinders in which siderosis occurred from prolonged exposure to finely divided iron dust. The metal was chrome vanadium and chrome molybdenum tool steel containing about 98 per cent iron, 2 per cent alloy and not more than 0.2 per cent silica, an amount too small to be a factor in the production of silicosis. The artificial abrasive wheels were composed partly of silicon carbide but these did not constitute a silicosis hazard. In the first case seen the impression from the roentgenogram was that the condition was simple silicosis with nodular predominance and the authors state that it is impossible to differentiate, by x-ray examination, between silicosis nodulation, the pseudo-nodulation of benign pneumoconiosis and the shadows cast by many pulmonary diseases unassociated with dust inhalation, such as metastatic cancer, Hodgkin's disease, miliary tuberculosis, lipid pneumonitis, fusospirochaetal disease, and various fungus infections. Differential diagnosis depends therefore upon a combination of clinical features, occupational history, physical examination and laboratory studies. Often an industrial engineering survey of the plant must be made in order to determine the nature, concentration and particle size of a suspected dust. The authors emphasize that benign pneumoconiosis produces nothing more than shadows cast on a skiagram. The responsibility to the workman and to industry for adequate distinction between the condition and silicosis or asbestosis is manifest, since advanced silicosis is usually disabling and, when complicated by tuberculosis, is fatal. Advanced asbestosis produces disability and ultimately reduction of pulmonary ventilation with cardiac failure.

Dunner, L. (1945) *Brit. J. Radiol.*, 18, 33.

Pendergrass, E. P., and Leopold, S. S. (1945) *J. Amer. med. Ass.*, 127, 701.

PNEUMONIA, LOBAR

See also B.E.M.P., Vol. IX, p. 713; and Cumulative Supplement, Key No. 1279.

Complications and sequelae

Other complications

Anaemia and hypoproteinaemia.—Armstrong and his colleagues report on the development of anaemia and hypoproteinaemia in a case of pneumonia. The patient, a man aged 38 years, was very ill with high fever, cough, cyanosis and dyspnoea. The sputum was rusty and contained type I pneumococci. There were signs of consolidation of the right lung. The patient failed to improve in spite of treatment with sulphonamides and specific antiserum. Penicillin was given from the tenth to the twenty-second day of the disease and, with this therapy, no more pneumococci could be detected by direct examination of the sputum. On the tenth day the plasma proteins were found to be 4.5 grammes per 100 cubic centimetres. The haematocrit level was 30. Intensive therapy with blood and plasma produced a rise of plasma proteins to 7.2 grammes per 100 cubic centimetres and a haematocrit reading of 40. Nearly all measures were employed which had the effect of maintaining the optimum gas exchange in the remaining functional lung tissue. The patient gradually recovered and, at the end of 3 months, physical and radiographic examinations showed no evidence of intrapulmonary disease. In another man, aged 85 years, pneumonia and pleural effusion developed after suprapubic prostatectomy. Blood tests revealed the presence of anaemia and hypoproteinaemia, but it was con-

sidered that these deficiencies had existed before the onset of the illness. Recovery ensued with treatment which included the administration of plasma, whole blood and amino acids, such treatment was essential for some time after the apparent bacteriological arrest of infection. It is concluded that in severe cases of pneumonia the onset of anaemia and hypoproteinaemia should be countered by the early use of whole blood and plasma together with an adequate intake of protein. The treatment must be guided by determinations of the amount of protein in the plasma.

Treatment

Specific treatment

Statistics of cases in which sulphonamide drugs were used—King Lewis discusses the prognosis and treatment of 127 children with pneumonia who were treated at Great Ormond Street Hospital for Children, London, with the sulphonamide group of drugs, and compares them with 100 children treated without sulphonamides during 1936–1938. The total mortality of the sulphonamide group was 9 per cent as compared with 18 per cent in the pre-sulphonamide group. Of the children under 6 months of age 8 out of 10 died in the pre-sulphonamide group whereas out of 27 of those treated with sulphonamides only 3 died. Three sulphonamides were used: sulphapyridine in 1939–1941, sulphapyridine and sulphadiazine in 1942 and Sulphamezathine (sulphadimethylpyrimidine, sulphamethazine) in 1943. The response to treatment was best estimated by the number of days which elapsed before patients were afebrile and improving. In the case of Sulphamezathine 63 per cent improved within 2 days and only 7.4 per cent failed to respond to the drug, in the case of sulphapyridine the corresponding percentages were 45 and 15.5 and in that of sulphadiazine, 46.2 and 7.7. The average duration of the febrile period of the pneumonia was 10.3 days in the pre-sulphonamide group and in the sulphonamide it was 3.2 days. A scheme of dosage is set out, for all ages up to 10 years, which corresponds approximately to $1\frac{1}{2}$ grains daily of either sulphapyridine or sulphadiazine or 2 grains daily of Sulphamezathine per pound of expected body weight.

Non specific treatment

Sulphapyridine in pneumococcal lobar pneumonia—Dick discusses the effect of great and small blood concentrations of sulphapyridine in the hospital treatment of pneumococcal lobar pneumonia. He reports on a series of 161 unselected cases of pneumococcal pneumonia in which all the patients received an initial dose of 2 grammes of sulphapyridine and then 1 gramme 4-hourly for 7 days. The amount of sulphapyridine was estimated in the blood the day after admission to hospital and each day following, the mean of the first three estimations being used to establish the mean blood level. Only 20 per cent of patients had a blood level over 60 milligrams per 100 cubic centimetres, but this low percentage might have been due to the patients' copious fluid intake. It was found that the temperature became normal in 48 hours in a slightly greater percentage when the blood level was high, but the difference disappeared at the end of 96 hours. Complications developed in 5 patients only and the incidence of these bore no relation to the blood level. Again, a high or low blood level did not appear to influence the final outcome since 17 patients—some of whom were very ill with an added bacteraemia—who had blood levels below 2 milligrams per 100 cubic centimetres, all made good recoveries, and the frequency of delayed resolutions was no greater. Dick concludes that although patients vary in their capacity to absorb the drug and consequently no reduction in the total dosage should be made, at the same time there is no reason to suppose that a high blood level will influence the prognosis, he advocates that the present standard dosage should be continued.

Armstrong, S. H., Jun., England, A. C., Jun., Favour, C. B., and Schenberg, I. H. (1945) *J. Amer. med. Ass.*, 127, 303.

Dick, A. (1945) *Lancet*, 1, 141.

King Lewis, F. L. (1944) *Arch. Dis. Childh.*, 19, 122.

POLIO MYELITIS AND POLIOENCEPHALITIS

See also B.E.M.P., Vol. X, p. 12, and Cumulative Supplement, Key No. 1282.

Pathogenesis

Enlarged tonsils and adenoids

Association with bulbar and bulbo-spinal types—Lucchesi and LaBocchetta analysed 432 cases of acute anterior poliomyelitis, admitted over a 6-year non-epidemic period to one Philadelphia hospital, in order to determine the relation of presence or absence of enlarged tonsils and adenoids to the type and mortality of the disease. They distinguished spinal, bulbar, bulbo-spinal and non-paralytic types, in relation to these, factors considered were season, race, sex and age. Twenty three of the total 30 cases of bulbar and 28 of the 48 cases of bulbo-spinal poliomyelitis occurred in the group of 165 patients who had had adenoido-tonsillectomy. Only 93 (30.9 per cent) of 319 patients with spinal poliomyelitis had had tonsillectomy. Non-paralytic poliomyelitis occurred approximately equally among the two groups. The greater incidence of bulbar and bulbo-spinal types in patients who had had adenoido-tonsillectomy was most pronounced in the 0–5 years age group, which was also the largest group (180 patients), of these 41 per cent of the tonsillectomized had bulbar involvement as against 8.1 per cent of those whose tonsils and adenoids had not been removed. Eighteen of the 432 patients died, 14 of whom (78 per cent) had had adenoido-tonsillectomy. Of these,

3 had bulbar, 10 bulbo-spinal and 5 spinal poliomyelitis, that is, mortality was 10.9 times greater in patients with than in patients without bulbar involvement. Approximately 66 per cent of all patients were males, whatever the type; mortality was equal among the sexes. From this evidence the authors infer that absence of pharyngeal lymphoid tissue increases the risk of bulbar involvement in persons with poliomyelitis. They deprecate indiscriminate removal of tonsils and adenoids, especially during the season (August–September) and in areas in which the incidence of poliomyelitis is abnormally great.

Immunity and resistance

Susceptibility

Resistance of cotton-rats to the virus.—Weaver describes the results of 11 experiments testing the effects of vitamin B complex-free diets, partial inanition and sex on resistance of cotton-rats to the virus of anterior poliomyelitis. The rats when 6 weeks old were separated into two groups according to sex and half of each group were fed on a vitamin B complex-free diet; the other half were used as controls. Two weeks later suspensions of the Armstrong-Lansing strain of poliomyelitis virus were introduced in varying quantities into either the cerebrum, stomach, colon, peritoneal cavity, nose, blood stream, subcutaneous tissue or beneath the pharyngeal mucosa of the rats in the experimental groups. If no symptoms developed during the next 25 days re-inoculation by 3 routes, namely intracerebral, subcutaneous and intranasal, was carried out and was repeated after a further 25 days if still no symptoms occurred. Rats remaining symptomless after this were considered to be immune. In a twelfth experiment intracerebral injections of virus were given to rats fed on or inoculated with varying quantities of vitamin B complex. The results of all these experiments did not produce any evidence to show that lack of vitamin B complex, partial inanition or sex, causes either increased or decreased susceptibility of cotton-rats to poliomyelitis. Neither do they support the theory that the virus is a biochemical by-product of vitamin B deficiency, and that poliomyelitis is a fulminant form of beri-beri. Again, the group fed on vitamin B complex showed essentially the same response to the virus as did the other groups, thus demonstrating that doses of vitamin B complex have no especial therapeutic or prophylactic value in the treatment of poliomyelitis.

Epidemiology

Nasopharynx

Observations on the virus invasion of mouth and pharynx.—Howe, Bodian and Wenner report observations on the presence of poliomyelitis virus in the human oro-pharynx in a further 36 cases, 20 from New Haven and 16 from Chicago. Sterile cotton swabs were lightly rubbed over the pharynx 1–9 days after the onset of the disease. From the swabs an inoculum was prepared and one half was introduced intercerebrally, through a trephine hole, into each lateral thalamus of a rhesus monkey. From the 36 cases virus was recovered in 10 (28 per cent). In the New Haven cases virus was isolated in 40 per cent because two-thirds of the swabs were obtained by the third day whereas in the Chicago cases two-thirds of the swabs were obtained between the fourth and ninth days. In no instance was virus isolated after the third day but 43 per cent showed recovery of virus if the swab was taken before that day. Virus was isolated from all bulbar paralytic cases during the first 3 days of illness. An improved technique might show a greater percentage of virus isolation in acute cases from pharyngeal swabbing similar to the increased percentage of positive isolation of faecal virus during the first 10 days of the disease which technical improvements have made possible in the last 5 years.

Treatment

The paralysis

Criticism of the Kenny technique.—A committee consisting of Ghormley and his colleagues investigated 740 patients with infantile paralysis, approximately 650 of whom had been treated by the Kenny method. In most cases the onset of illness had occurred since 1940. The committee concedes that the publicity attached to the treatment has brought about renewed interest in certain principles evolved by the medical profession and subsequently claimed as original by Miss Kenny. In 1911 Robert Jones described stretch paralysis and functional loss of use due to pain, phenomena which Pohl and Kenny ascribe, less scientifically, to loss of ability to contract flaccid muscles due to functional dissociation from the nervous system, otherwise known as mental alienation. Miss Kenny was not the first to diagnose the disease in the preparalytic stage or to describe muscle incoordination, and maintenance of correct posture has been standard practice for over 30 years. The Kenny method employs moist heat, muscle training and pools, all of which were advocated by Lovett in 1917. Miss Kenny denies the value of respirators in cases of respiratory embarrassment and condemns the use of splints or braces in spite of the fact that splints have been applied to control contractures developing in patients treated by her method. Moreover, some of these patients have had to use crutches instead of braces. The committee disagrees with the assertions that muscle spasm is the primary lesion and that nerve cell death rarely causes paralysis. If deformities are prevented the flaccid paralysis due to destruction of nerve cells is the most important cause of crippling. There is not any evidence that early local treatment in the preparalytic stage will control pain and prevent paralysis. Active treatment during the acute febrile stage can be detrimental and movements of the extremities are satisfactory procedures only when carried out within the range of comfort. Continuous hot packs are not needed in order to relieve.

spasm or pain. In some of the cases examined the paralysis became worse after the institution of the Kenny treatment but further observation is required to determine the effect on paralytic scoliosis. Miss Kenny claims that over 80 per cent of her patients recover compared with 13 per cent of those who are treated by orthodox means. The latter figure is based on an article which dealt entirely with severely paralysed patients. Any assessment of the results of treatment should take account of the fact that spontaneous recovery may ensue in from 50 to 80 per cent of cases.

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PREGNANCY: NORMAL AND PATHOLOGICAL

See also B E M P, Vol. X, p. 48, and Cumulative Supplement, Key Nos. 1291-1303

Diagnosis of pregnancy

Signs

Radiographical evidence—Hartley reviews the present use of radiology in obstetrics, in order to indicate in broad outline a general plan for the future of radiology in this field. At present, accuracy may reasonably be expected in demonstration of maturity, presentation, position, viability and deformities of the fetus, of the size and shape of the uterus, in pelvimetry and in descending pyelography. In other types of examination the radiographical report cannot be guaranteed to be accurate. For example, there are fallacies in soft tissue radiography of the placenta. Nor can the presence of pelvic or uterine tumours together with pregnancy always be recognized. Lesser fetal defects may not be diagnosed. Antenatal recognition of conditions incompatible with life may, by modification of the obstetrical approach, reduce maternal mortality. Certain technical advances are awaited: a rotating anode tube of fine focus, a fine stationary grid of Schonander type, an improved Potter-Bucky grid, a selective radio-opaque medium for placentography, a technique for outlining tumours and a sex indicator. The association of spina bifida with skull defects requires investigation since these defects occur in 1 per cent of births. Fetal mortality may be diminished by radiological examinations of abortions and stillbirths. There are possibilities in mass radiography of primiparae and live infants. The writer visualizes closer collaboration between accoucheurs, obstetricians, paediatricians and radiologists, the linking up of radiological and pathological departments with antenatal centres and obstetric units, the universal provision of adequate apparatus and of specially trained staff for routine and research work and the establishment of a national and international bureau for the purpose of tracing the history of families from generation to generation.

Tests

The 6 hour rat test for pregnancy—Kline reports on the Salmon, Geist, Salmon, Frank 6-hour rat test for pregnancy—a modification of the Eberson and Silverberg and Frank and Berman tests—which had been found to be reliable and much simpler than the Friedman test. At Mount Sinai Hospital, Cleveland, 432 tests were made on 401 specimens, and 1,011 immature rats were used, 2 or more for each test. Of the 482 rats in the positive tests 13 were refractory. The earliest positive tests in the series were obtained in a case of uterine pregnancy 8 days after the missed period, and in a case of ectopic pregnancy 2 days after what had been thought to be the onset of menstruation. The rat test was negative in 3 cases of very early pregnancy and was doubtful in 3 others, but a later specimen of urine in the 6 cases gave a positive reaction. Specimens from 8 non-pregnant women gave doubtful reactions, and in one patient clinically considered not to be pregnant a positive reaction was obtained. In 2 cases of ectopic pregnancy the test was positive and in a third case it was negative 10 and 12 days after a missed period.

Haemorrhages

Unavoidable haemorrhage from placenta praevia

Radiography in the diagnosis—McCort, Davidson and Walton discuss the value of radiographical investigation in cases of bleeding occurring during the last three months of pregnancy. If haemorrhage is not too severe, this is the first diagnostic test to be made after the admission of the patient to hospital. Large x-ray films are used and the abdomen is viewed in the lateral and anteroposterior positions. The technique involved in visualizing the uterine wall includes an exposure of 300 milliampere-seconds at a distance of 36 inches, removal of all filtration and the employment of an intensifying screen and the Potter-Bucky diaphragm. The kilovoltage varies with the thickness of the patient. Failure to visualize the placenta in the body of the uterus suggests the diagnosis of central placenta praevia, but some other in cause for the bleeding must be considered should the greatest width of the placenta be seen in the fundus or lateral wall. In vertex presentations evidence of anterior or posterior placental physis pubis or sacral promontory. A placenta situated on the posterior wall produces displacement of the fetal head from the mid-coronal and sagittal planes, an accurate diagnostic suggestion by Hall and Golden but not applied by the authors. Doubtful cases require

pneumocystography with an intravesical injection of approximately 250 cubic centimetres of air. Widening of the vesicocephalic distance occurs in anterior implantation, and a lateral placental site is associated with displacement of the bladder to one side. The examinations yielded accurate results in 87.8 per cent of 132 patients. The method was found to be correct in 97 per cent of the cases diagnosed as negative for placenta praevia, but relatively poor results were obtained in the investigation of marginal placenta praevia and low implantations.

Treatment

General principles in unavoidable haemorrhage.—Bell recapitulates the signs and symptoms of diagnostic importance in haemorrhage in late pregnancy. The only sure way to diagnose placenta praevia is by vaginal examination, but this should not be undertaken until the patient is in surroundings when everything is available to stop haemorrhage. In treatment, Caesarean section should never be performed after plugging the vagina or after severe bleeding. The ideal case for operation is the elderly primipara not in labour, with a well developed fetus, who has a central placenta praevia. The simplest method of arresting bleeding is artificial rupture of the membranes and the application of an abdominal binder. Whether this or other methods are used, such as Willett's scalp forceps, vaginal plugging or bipolar version, replacement of blood is vital. Delivery should not be hastened until shock has been overcome and the use of forceps should be avoided if possible owing to the vascular lower segment placental site. A small loss in the third stage may prove to be fatal to a patient already in a condition of shock and who has lost blood. Blood of a compatible ABO group, preferably Rh negative, should be readily available. Slight accidental haemorrhage may be treated expectantly by rest and sedatives. If the haemorrhage is severe and labour has not begun, the patient should be anaesthetized, the membrane ruptured and the vagina plugged with rolls of gauze soaked in 5 per cent Dettol solution. If labour has started, rupture of the membranes, plugging, or small repeated doses of pituitary extract may be necessary. If the tone of the uterus cannot be recovered in concealed haemorrhage, Caesarean section may offer the only chance.

Toxaemias of late pregnancy

Pre-eclamptic toxæmia and eclampsia

Significance of oedema, hypertension and albuminuria.—In discussing the significance of oedema, hypertension and albuminuria in toxæmia of pregnancy, Browne emphasizes that antenatal supervision provides unique opportunities for studying the order of development of these symptoms in relation to each other; such knowledge is necessary before conclusions can be reached about the meaning and genesis of the symptoms and is of importance to general pathology. Oedema, according to the author, sometimes but not always precedes hypertension as the earliest sign of toxæmia, and in the causation of eclamptic fits is complementary to hypertension. The part played by increased capillary permeability and by hypoproteinaemia, particularly when it appears after heavy albuminuria, is discussed in considering the genesis of oedema. Pregnant women's tissues have an avidity for water. In this connexion the significance of progesterin and oestrin is doubtful, but their close chemical relationship to the suprarenal cortical hormones is noted. Administration of desoxycorticosterone (desoxycortone) in several reported cases caused retention of salt and water and development of oedema and hypertension. Whatever the cause of oedema its development can be controlled by limiting salt intake. Browne defines the standard of normal blood pressure as 120/80. Recent experimental evidence indicates that the hypertension of pre-eclampsia is due to a humoral, not a nervous, mechanism, and that it is not due to renal ischaemia, however produced, nor to hypertensin, tyramine or adrenaline. During her pregnancy, evidently after the third month, the woman in whom pre-eclampsia develops acquires a sensitivity to the action of certain pressor substances which is unattributable to constitutional predisposition. Albuminuria, Browne believes, never precedes hypertension or oedema. Its cause is that arteriolar spasm accompanying pre-eclamptic hypertension produces anoxia of the glomerular capillaries which become abnormally permeable, allowing protein leakage. That this may not be the sole cause of albuminuria is suggested by a reported case of accidental haemorrhage with associated albuminuria in which there was slight evidence of previous hypertension but a history of preceding shock.

Importance of close supervision and strict routine.—Arnell describes an ultraconservative plan of management employed in 142 personally supervised cases of eclampsia, without one fatality. He attributes the success to constant observation of each patient by an experienced staff throughout the entire course of treatment, which permitted careful integration of the various therapeutic components—in themselves neither new nor original—into an individualized regimen. During the convulsive stage the chief measures were: (1) frequent changes of posture; (2) aspiration and continuous oxygen administration; (3) limitation of sedation to the dosage necessary to control convulsions and hyperirritability; (4) dextrose solution given intravenously in the smallest amounts required to produce an hourly urinary output of 25 cubic centimetres, with a return to a minimum daily fluid intake orally of 4,000 cubic centimetres as soon as the patient could swallow. A salt-free diet providing 100 grammes of protein was prescribed, since dietary investigations in 62 patients suggested that protein deficiency might be aetiologicaly significant in this series, although lack of adequate prophylaxis was the chief aetiological factor. During the controlled eclamptic state, rest in bed and constant observation were continued. Termination of pregnancy, unless ensuing spontaneously, was delayed until optimum recovery from the acute stage had occurred. Labour

was induced with a minimal amount of trauma, medical induction being repeated once or oftener if required. Local analgesia was used for all types of operative delivery. Caesarean section was done in 9 cases, in only 4 of which was eclampsia itself the indication for the procedure. From his observation of 85 patients at intervals of from 5 to 12 weeks after delivery, of 46 patients at intervals of from 1 to 5 years after delivery, and of 34 patients in 56 subsequent pregnancies, Arnell claims that this therapeutic regimen in no way jeopardized either the patients' future health or their subsequent pregnancies. The incidence of residua in the group of 25 patients who were delivered more than 7 days after the onset of their convulsions, was no greater than it was in the whole group under subsequent surveillance. The fetal case fatality was 24.2 per cent, but improved to 17.6 per cent in the last 51 cases, when the policy of greater consideration for the baby was increasingly followed.

Aetiology and pathogenesis

Review of possible causes—There is probably no single cause for the group of diseases classed under the heading of "toxaemia of pregnancy" and the various manifestations of the condition do not admit of a logical scheme of correlation. Stacey points out that albuminuria of pregnancy may lead to permanent vascular and renal damage and to death of the fetus, but it does not often give rise to the most serious sequel of toxaemia, namely eclampsia, without passing first into the condition described as pre-eclamptic toxaemia. Eclampsia may occur without any rise of blood pressure, albuminuria or oedema preceding the convulsions. Furthermore, the relationship between placental haemorrhage and toxaemia is not clear and toxic signs may be associated with an abnormally situated placenta and not only, as is commonly believed, with haemorrhage from one normally situated. In the treatment of toxaemia of pregnancy, rest in bed is of prime importance in order to diminish the metabolic processes in the body and in order to keep down oedema, which is one of the factors apparently so necessary to the production of eclampsia. A diet should be instituted which is balanced in relation to water intake and output and is largely salt free. Low protein diets are not advisable and the daily calorie intake should be brought by stages to about 3,000 calories. In all cases of pre-eclamptic toxaemia labour should be promptly induced. The convulsions of eclampsia are best controlled by the synergistic action of subcutaneously injected magnesium sulphate with morphine, and labour should be induced if it has not already begun 48 hours after the last fit. Stacey draws attention to the occurrence of albuminuria and transient oedema due to anaemia in pregnancy, which became more prevalent during the years of the recent war and which leads often to a mistaken diagnosis of toxaemia and consequent mismanagement of treatment.

Diseases of the cardiovascular system

Heart disease

Management of pregnancy in serious rheumatic disease—Mendelson, describing the management of pregnancy and delivery complicated by serious rheumatic heart disease, gives data based on treatment of 1,089 cases with a mortality of 8 (0.7 per cent) due to the cardiac condition, 5 of the deaths occurred *ante-partum* and 3 *post-partum* and all were due to decompensation. Of the former, one occurred at the fifth, one at the sixth, 2 at the seventh and one at the ninth month, 2 of the patients had been discharged from hospital after recovery from an earlier episode of cardiac failure. The author emphasizes that such patients should remain in hospital, under observation for the remainder of pregnancy. Of the 3 *post-partum* deaths, one occurred after hysterotomy and 2 after Caesarean section. The data presented by the author suggest modification of the views that cardiac patients have short labours or a greater than normal blood loss at parturition or an unusual tendency to spontaneous abortion or premature labour. Mendelson attributes the relatively low mortality described, to very meticulous management both medical and surgical of the pregnancies, as well as of the treatment of cardiac cases in early pregnancy, is a relatively safe procedure and that abdominal delivery at term is not often necessary. He says that elevation of pulse rate above 110 and respiratory rate above 24, or of the pulse alone, during the first stage of labour, gives ample warning of the approach of cardiac failure.

Embolism

Air embolism after douching—Forbes reviews the causes of air embolism and describes a case of accidental death due to air embolism as a complication of vaginal douching in pregnancy. Quite small veins may serve as a portal of entry, especially when the air is under pressure as is shown by the reported cases of air embolism after antral lavage, distension of the bladder and urethra with air, and therapeutic vaginal insufflation. If the air enters the pulmonary circulation, Forbes states that the question has not yet been settled whether death results from mechanical interference with heart function, or from blockage of the pulmonary artery with froth, or from multiple emboli in the pulmonary arterioles. There is no general agreement concerning the amount of air which will cause death. The author reports on a case of sudden unexplained death in a multipara aged 34, who had begun to menstruate the day before death. At necropsy a retroverted gravid uterus was found, in which there was a 1 inch of the lower edge. The right heart was dilated and filled with frothy blood. The lungs were very oedematous, sections showing areas of infarction. These findings indicate that air embolism was the cause of death. Subsequent enquiry showed that a menstrual period had

there was a corrected salvage rate of 85 per cent. Among 43 pregnant women receiving various schedules of massive Mapharsen therapy, 1 died from arsenical encephalopathy after 5 injections of the drug. At the same clinic, prior to institution of massive arsenotherapy, 34 pregnant women with early infective syphilis received routine therapy, 3 being treated with Mapharsen, 8 with arsphenamine and 23 with neoarsphenamine. Of these, 1 died from arsenical encephalopathy after 2 doses of neoarsphenamine, jaundice developed in 5 and exfoliative dermatitis in 1, 50 per cent delivered syphilitic babies. None of the babies of 23 untreated patients with early infective syphilis, escaped the disease. No relationship was noted between the results obtained and the time during pregnancy when intensive treatment was begun. Of 32 patients who became pregnant after having had intensive therapy for early syphilis and who received no further treatment, 5 had spontaneous abortions, of which only 1 was attributable to syphilis. Although in the authors' experience intensive therapy proved to be less toxic and more effective than was routine therapy, the risk, which remains, of producing arsenical encephalopathy emphasizes the need for caution in the use of arsenical drugs when syphilis in pregnancy is being treated.

Wassermann and Kahn tests

Report on a series of 28,924 cases—Hughes reports on Wassermann and Kahn tests on 28,924 pregnant women with an incidence of 160 positives (0.55 per cent). He refers to a survey in 1935 which showed that 6 per cent of 62,516 patients attending 64 antenatal clinics were syphilitic and quotes Potter and Adair's statement that spirochaetes have not been demonstrated in the placenta or fetus before the fifth month of gestation, that infection probably does not occur until about this time and that it is not a common cause of early abortion but contributes to fetal mortality in the last half of pregnancy. Of the 160 patients the results of the pregnancies were known in 134 cases. The patients all had antisyphilitic treatment of adequacy depending upon how early in pregnancy they reported to the antenatal department. One hundred and twenty infants were born alive, 8 were still born and 4 died in the neonatal period. There were 2 miscarriages, giving a combined stillbirth and neonatal death rate of 10 per cent, in contrast to a figure of 24 per cent calculated from data of the previous obstetric history of 98 multiparae. The author urges that, under present conditions especially, a Wassermann test should form part of all routine antenatal examinations.

Ectopic pregnancy

Primary abdominal pregnancy

Review of literature—Gardner and Middlebrook review the subject of abdominal pregnancy, basing their survey on 236 cases analysed previously by Cornell and Lash in 1933 and 22 more from the literature. The incidence of abdominal pregnancy is higher above the thirtieth year and occurs most often in first and second pregnancies. There is no way of predicting its likelihood from data of previous pregnancies. About 80 per cent of the patients had amenorrhoea for at least 6 months before the diagnosis was made but the authors find it impossible to assess the relative incidence of primary abdominal pregnancy, namely, that in which evidences of origin from a primary intra uterine or intratubal position were absent. Diagnosis was made by the general history of impregnation, signs, symptoms and laboratory tests associated with early signs and symptoms of tubal or other rupture phenomena with pain and bleeding and the results of examination. There were usually a sensitive abdomen with an easily felt fetus and a loud fetal heart. The fetus was usually in the transverse position. On vaginal examination the cervix was found to be high and displaced or very low, and the abdominal mass was separate from the uterus. Lipiodol visualization was often used for the purpose of confirming these findings and abdominal x-ray often revealed unusual position of the fetal limbs. Abdominal pregnancy is seldom complicated by other diseases, including the toxæmias of pregnancy. Most authorities believe that the best time to operate is the thirty-sixth week. After this time rupture of the sac, separation of the placenta with haemorrhage and infection and death of the fetus all occur more often. Laparotomy is the method of choice. The whole or parts of the placenta may be left in the abdomen with little risk of infection or haemorrhage. The authors report on a case of full term abdominal pregnancy with surviving mother and healthy child free from the deformities usually associated with the condition.

Supracervical pregnancy

Stanley Brown and Shields report on a case of supracervical pregnancy occurring after supravaginal hysterectomy. The patient had had two previous pregnancies which were normal apart from early nausea and vomiting. Later, supracervical hysterectomy was performed for removal of a fibroid. The cervical stump was closed with 4 interrupted chromic sutures, the ligated tubes and ligaments were sutured to its posterior lip and the vesical fold was brought over this area. Subsequently the patient had scanty, fairly regular monthly bleeding until 9 months later, when she missed one period, was nauseated and had occasional lower abdominal pain. Examination at that time revealed nothing abnormal, but a month later a small soft mass felt above the softened cervix was diagnosed as a supravaginal pregnancy of about 6 weeks. Exploratory laparotomy through the old midline scar was performed and the vesicle fold with the round ligaments and tubes was found to be stretched upwards by a mass situated apparently on the cervical stump. Beneath the fold lay tissue resembling placenta from which a sac of fluid containing a 6½ weeks' embryo was dissected out intact. Placental tissue was

removed as far as was possible, both tubes were resected and the round ligaments were resutured to the posterior lip of the sutured cervical stump. Recovery was uneventful.

Treatment

Evans discusses the diagnosis and treatment of ectopic gestation. A history of amenorrhoea is not always obtainable. In the rarely seen stage before tubal rupture or abortion, the symptoms are indefinite pains on one side, slight vaginal bleeding, tenderness and, possibly, a soft swelling in one lateral fornix. Salpingectomy is usually indicated. After profuse intra-abdominal haemorrhage there is a history of sudden acute abdominal pain, often accompanied by vomiting and faintness, hypogastric and possibly shoulder-tip pain. The patient is collapsed, with small rapid pulse and subnormal temperature, and tender flaccid abdomen. Vaginally, there is tenderness of the pelvic peritoneum and a swelling in one lateral fornix. Immediate restorative measures, especially blood transfusion, and prompt laparotomy under gas and oxygen, ether or even local anaesthesia, is imperative. Most diagnostic difficulties occur in those cases which are seen after less severe haemorrhage. The symptoms may include weakness, abdominal pain, vaginal haemorrhage or possibly urinary retention due to a pelvic haematocoele formed as a result of repeated small haemorrhages. The signs include anaemia, slight pyrexia and tachycardia, fullness of the lower abdomen, and tenderness on vaginal examination, which also shows fullness in one or both lateral fornices. Evans discusses the differential diagnosis of these cases from uterine abortion—in which chorionic villi but neither swelling nor tenderness in the lateral fornices can be demonstrated—retroverted gravid uterus, pyosalpinx and appendicitis. In doubtful cases of appendicitis, laparotomy is indicated. Treatment is either salpingo-oophorectomy or, if there is an infected pelvic haematocoele, posterior colpotomy and drainage. At any stage, prompt admission to hospital is essential.

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PREMATURITY

See also B.E.M.P., Vol. X, p. 126.

General management and feeding

Preparation of feeds

Crosse considers that in the care of larger premature infants good results can be obtained in the child's own home. Smaller babies should be removed to a hospital in which there are special facilities to deal with the numerous complications that may arise. The main principles of treatment depend upon maintenance of the body heat and respiration, careful feeding, protection from infection and the early recognition of complications notably from renal, alimentary and hepatic dysfunction, failure in mineral and vitamin storage and increased capillary fragility. Smaller babies tend to stabilize their temperatures at 96° F., the level gradually rising to 98° F. with increasing weight. The smallest infants require a cot temperature of 90–95° F. and clothing should be designed to conserve body heat. Oxygen and carbon dioxide may be needed to assist respiration. If the infant can suck it is put to the breast or bottle. If it cannot suck but can swallow, it is fed by pipette. If it can neither suck nor swallow, tube feeds are given by means of a Jaques catheter in the oesophagus. Feeds should not be given for at least 12 hours after birth owing to incoordination of the swallowing reflex. Few premature babies can digest more than 1.5–2 per cent fat in an artificial feed. The protein can be made more digestible by being boiled, by dilution with water, by peptonization or by acidification. By the age of 2 weeks the protein content of the feed should be about 2 per cent and cane or beet sugar content 8–10 per cent. Extra vitamins must be given to all premature babies, particularly vitamins A, D and C. In order to prevent the hypoproteinaemia which occurs, synthetic vitamin K may be given after birth. It is advisable to give syrup of calcium lactophosphate, 1 minim per pound of body weight, daily from the end of the second week.

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Review of literature—Gardner and Middlebrook review the subject of abdominal pregnancy, basing their survey on 236 cases analysed previously by Cornell and Lash in 1933 and 22 more from the literature. The incidence of abdominal pregnancy is higher above the thirtieth year and occurs most often in first and second pregnancies. There is no way of predicting its likelihood from data of previous pregnancies. About 80 per cent of the patients had amenorrhoea for at least 6 months before the diagnosis was made but the authors find it impossible to assess the relative incidence of primary abdominal pregnancy, namely, that in which evidences of origin from a primary intra uterine or intratubal position were absent. Diagnosis was made by the general history of impregnation, signs, symptoms and laboratory tests associated with early signs and symptoms of tubal or other rupture phenomena with pain and bleeding, and the results of examination. There were usually a sensitive abdomen with an easily felt fetus and a loud fetal heart. The fetus was usually in the transverse position. On vaginal examination the cervix was found to be high and displaced or very low, and the abdominal mass was separate from the uterus. Lipiodol visualization was often used for the purpose of confirming these findings and abdominal x ray often revealed unusual position of the fetal limbs. Abdominal pregnancy is seldom complicated by other diseases, including the toxæmias of pregnancy. Most authorities believe that the best time to operate is the thirty-sixth week. After this time, rupture of the sac, separation of the placenta with haemorrhage and infection and death of the fetus all occur more often. Laparotomy is the method of choice. The whole or parts of the placenta may be left in the abdomen with little risk of infection or haemorrhage. The authors report on a case of full-term abdominal pregnancy with surviving mother and healthy child free from the deformities usually associated with the condition.

Supracervical pregnancy

Stanley Brown and Shields report on a case of supracervical pregnancy occurring after supravaginal hysterectomy. The patient had had two previous pregnancies which were normal apart from early nausea and vomiting. Later, supracervical hysterectomy was performed for removal of a fibroid. The cervical stump was closed with 4 interrupted chromic sutures, the ligated tubes and ligaments were sutured to its posterior lip and the vesical fold was brought over this area. Subsequently the patient had scanty, fairly regular monthly bleeding until 9 months later, when she missed one period, was nauseated and had occasional lower abdominal pain. Examination at that time revealed nothing abnormal, but a month later a small soft mass felt above the softened cervix was diagnosed as a supravaginal pregnancy of about 6 weeks. Exploratory laparotomy through the old midline scar was performed and the vesicle found with the round ligaments and tubes was found to be stretched upwards by a mass situated apparently on the cervical stump. Beneath the fold lay tissue resembling placenta from which a sac of fluid containing a 6½ weeks' embryo was dissected out intact. Placental tissue was

removed as far as was possible, both tubes were resected and the round ligaments were resutured to the posterior lip of the sutured cervical stump. Recovery was uneventful.

Treatment

Evans discusses the diagnosis and treatment of ectopic gestation. A history of amenorrhoea is not always obtainable. In the rarely seen stage before tubal rupture or abortion, the symptoms are indefinite pains on one side, slight vaginal bleeding, tenderness and, possibly, a soft swelling in one lateral fornix. Salpingectomy is usually indicated. After profuse intra-abdominal haemorrhage there is a history of sudden acute abdominal pain, often accompanied by vomiting and faintness, hypogastric and possibly shoulder-tip pain. The patient is collapsed, with small rapid pulse and subnormal temperature, and tender flaccid abdomen. Vaginally, there is tenderness of the pelvic peritoneum and a swelling in one lateral fornix. Immediate restorative measures, especially blood transfusion, and prompt laparotomy under gas and oxygen, ether or even local anaesthesia, is imperative. Most diagnostic difficulties occur in those cases which are seen after less severe haemorrhage. The symptoms may include weakness, abdominal pain, vaginal haemorrhage or possibly urinary retention due to a pelvic haematocoele formed as a result of repeated small haemorrhages. The signs include anaemia, slight pyrexia and tachycardia, fullness of the lower abdomen, and tenderness on vaginal examination, which also shows fullness in one or both lateral fornices. Evans discusses the differential diagnosis of these cases from uterine abortion—in which chorionic villi but neither swelling nor tenderness in the lateral fornices can be demonstrated—retroverted gravid uterus, pyosalpinx and appendicitis. In doubtful cases of appendicitis, laparotomy is indicated. Treatment is either salpingo-oophorectomy or, if there is an infected pelvic haematocoele, posterior colpotomy and drainage. At any stage, prompt admission to hospital is essential.

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PREMATURITY

See also B.E.M.P., Vol. X, p. 126.

General management and feeding

Preparation of feeds

Crosse considers that in the care of larger premature infants good results can be obtained in the child's own home. Smaller babies should be removed to a hospital in which there are special facilities to deal with the numerous complications that may arise. The main principles of treatment depend upon maintenance of the body heat and respiration, careful feeding, protection from infection and the early recognition of complications notably from renal, alimentary and hepatic dysfunction, failure in mineral and vitamin storage and increased capillary fragility. Smaller babies tend to stabilize their temperatures at 96° F., the level gradually rising to 98° F. with increasing weight. The smallest infants require a cot temperature of 90–95° F. and clothing should be designed to conserve body heat. Oxygen and carbon dioxide may be needed to assist respiration. If the infant can suck it is put to the breast or bottle. If it cannot suck but can swallow, it is fed by pipette. If it can neither suck nor swallow, tube feeds are given by means of a Jaques catheter in the oesophagus. Feeds should not be given for at least 12 hours after birth owing to incoordination of the swallowing reflex. Few premature babies can digest more than 1.5–2 per cent fat in an artificial feed. The protein can be made more digestible by being boiled, by dilution with water, by peptonization or by acidification. By the age of 2 weeks the protein content of the feed should be about 2 per cent and cane or beet sugar content 8–10 per cent. Extra vitamins must be given to all premature babies, particularly vitamins A, D and C. In order to prevent the hypoprothrombinaemia which occurs, synthetic vitamin K may be given after birth. It is advisable to give syrup of calcium lactophosphate, 1 minim per pound of body weight, daily from the end of the second week.

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203.

r. J. Dis. Child., 68, 190.

232; and Cumulative Supplement, Key Nos. 1315-1317.

—Epstein discusses the aetiology, pathology and treatment of the condition. In the definition of the condition is an absence of a psychosis. Moreover, the experience of combat must be sufficiently serious. Other criteria include a rapid onset of irritability resembling a relatively quick cure in the acute cases. Most patients have been exposed to a series of untoward experiences. These

Telegrams: Menformon, Rand, London

in 130 cases of prostatic carcinoma, subsequently kept under observation for periods up to 2½ years. Results included 42 dead, no appreciable change in 14, deterioration in 34, in 20 cases, despite clinical improvement, the disease was advancing. In 17 cases only did clinical improvement coincide either with apparent temporary arrest or regression of the disease. Of 65 patients with metastases, 83 per cent improved during the first 4 months, but after 2 years only 11 per cent had sustained the improvement, whereas the corresponding ratios of improved cases in the non metastatic group were respectively 54 and 36 per cent. Therefore Herger and Sauer suggest that the occurrence of delayed failures becomes increasingly probable in the remaining patients. They analyse the effects of androgen control therapy on the primary lesion on urinary obstruction, on weight, on erythrocyte count, on pain due to skeletal metastases, on metastatic lesions, and on serum acid phosphatase. Six patients with metastases in the lymphatic glands improved best, but the roentgenological appearances of bone metastases improved in only 4 of 59 cases. Metastases developed in patients with previously non metastatic disease, even after lengthy androgen control therapy. The authors conclude that castration should be reserved for patients with metastatic disease or with rapidly enlarging primary lesions. Exclusive oestrogen treatment is indicated for operable cases in which surgery has been refused, and for patients with moderately advanced, relatively asymptomatic lesions of apparent low grade malignancy. In Herger's and Sauer's experience failures occurring after exclusive stilboestrol administration benefited, at least temporarily, from orchidectomy. Oestrogen given to failures after orchidectomy was usually ineffective. In 22 patients manifesting resurgent symptoms, application of x-rays to the hypophysis in an attempt to decrease the activity of possible extragonadal sources of androgens, accomplished some degree of palliation, but was less effective as a palliative measure than was androgen control therapy.

Dieting and oestrogens—Herbst records observations on the therapeutic effects on 16 cases of carcinoma of the prostate of castration, administration by various routes of oestrogenic substances and a high calorie and vitamin but low cholesterol diet. It is claimed that high cholesterol diets accelerate and low cholesterol diets decrease the rate of cancer growth. These methods the author describes as the "chemical" treatment of carcinoma which he defines as such modification of the soil as will so inhibit the malignant process as to prevent it damaging the host. Zondek, Sulman and Sklow have shown that oestrogenic substances are very rapidly but diethylstilboestrol (stilboestrol) is very slowly, destroyed by the liver. Reable dosage of oestrogens for any individual should be the smallest effective amount, parenteral oestrogens will restore control of pain and symptoms, in rare instances, however, oestrogens not merely fail to inhibit but even apparently stimulate the malignant process. Vitamins not only improve general condition but also help to relieve pain, as do x rays in small doses one case only, failed to control the malignant process. X-ray treatment of the supraprenal glands has not yet been tried by the author. Extensive metastases are not always accompanied by raised blood phosphatase. No uniformity in the supraprenal glands was noted at a necropsy in the course of which the hypophysis was not investigated.

Hormonal treatment of prostatic carcinoma—Trainer discusses the principles involved in hormonal treatment of prostatic carcinoma. In health, oestrogen and androgen work in harmonious antagonism. Overaction of testosterone produces proliferation of prostatic epithelium, which may progress to metaplasia. When testosterone is withdrawn as by castration, or when its action is more than counterbalanced by administration of stilboestrol, regressive prostatic changes occur. The normal blood level of acid phosphatase, an enzyme found in large amounts in the prostate, is from 0.5 to 2 King Armstrong units. A rise to above 2.5 units is very suggestive of a prostatic carcinoma which has broken its capsule and especially of one which has metastasized. Administration of oestrogen or castration usually lowers the acid phosphatase blood concentration. The effects of withdrawal of androgen or of androgen neutralization are, clinically, striking amelioration of the local and general symptoms of prostatic carcinoma. Radiological examination may show regression of metastases. Hormonal treatment is not curative, however, and radical perineal prostatectomy is still indicated for operable growths. The only indication for stilboestrol therapy alone is in treatment of patients too ill for operation. A scheme of treatment is presented consisting of orchidectomy followed by a fairly intensive course of stilboestrol. The acid phosphatase blood level, estimated at intervals, is the best guide to the maintenance stilboestrol dosage required after the first intensive course. Orchidectomy alone will not remove all the androgen, extragonadal sources of which remain, as for example in the supraprenal glands. The duration of stilboestrol administration depends upon the radiological findings.

Plasma acid phosphatase estimation and subsequent stilboestrol therapy—Watkinson, Delory, King and Haddow describe estimations of plasma acid phosphatase in 10 cases of carcinoma of the prostate and the effect of treatment with stilboestrol. Six patients had raised acid phosphatase, 5 of these evinced radiographical evidence of bone metastases. Under stilboestrol treatment plasma acid phosphatase fell abruptly to the normal and was maintained for some time with a rise in alkaline phosphatase and then a gradual fall. At first large doses, up to 525 milligrams intramuscularly in 21 days, were administered, but they appeared to cause

oedema of legs, scrotum, penis and abdominal wall. Later 5 milligrams once or twice daily were used. In 4 of the patients, who had received previous high-voltage treatment, no alteration in the prostate was defined; in only 4 others was distinct regression of the primary tumour detected. Three patients had palpable lymphatic spread and oedema of legs; regression of secondary masses and reduction of oedema occurred under stilboestrol treatment. Nine patients experienced improved appetite and gained weight; frequency of micturition was lessened. Diminution of pain referred to bone was difficult to assess since rest alone ameliorates it, but in 4 cases the patients experienced partial or complete relief. Bone metastases increased in size, density or number under stilboestrol treatment.

Rationale of hormone treatment.—Buchwald and Hudson describe experiments relating to the biochemical processes which are involved in the hormone treatment of carcinoma of the prostate. Rats were injected with stilboestrol and testosterone propionate in order to study the effect on the metabolism of calcium and phosphorus. It was found that the serum phosphorus was not influenced by testosterone propionate but that stilboestrol produced a decrease in males approximately to the level of the serum phosphorus in normal females. Stilboestrol and testosterone propionate had no effect on the serum calcium or on the excretion of calcium or phosphorus. There was a noticeable decrease in the serum acid phosphatase of males which were injected with stilboestrol, a reduction similar to that produced by stilboestrol in patients with metastatic carcinoma of the prostate. The serum alkaline phosphatase was unaffected. A reduction was manifested in the activity of alkaline phosphatase in the femur and this phenomenon may have a bearing on the lack of healing of bony metastases in carcinoma of the prostate. Testosterone propionate increased the activity of the serum alkaline phosphatase of females. This indicates stimulation of growth since, in young children whose rate of growth is rapid, the activity of the serum alkaline phosphatase is slightly higher than it is in adults.

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PSYCHIATRY OF CHILDREN

See also B.E.M.P., Vol. X, p. 203.

Clinical forms

Gastro-intestinal

Encopresis in children.—Lehman discusses encopresis—psychological incontinence of faeces—in children, and describes 4 cases. Some authorities still think encopresis is caused by some physical abnormality, although many now consider the abnormality to be psychogenic in origin. Of the psychological causes lack of parental love is one of the most potent. This was present in varying degrees in the 4 cases described, in 2 of the cases being precipitated by the birth of a younger sibling. Encopresis frequently occurs in orphanages, and often a well-trained child will relapse when he is placed in a new home until he becomes fond of the new foster-mother. The break-up of families in Great Britain during the present war, due to evacuation, has caused many cases of encopresis. Extreme ideas and attitude of mind of the parents may cause stress to the child and he may also have to face difficult conditions in school. In 2 of the described cases the mothers were very exacting and domineering. Anxiety, anal eroticism and abnormal fears such as toilet phobia, are other causes. Psychological treatment is the only treatment of value, medicinal and physical treatment being of little use; rewards and punishments do more harm than good. Good relations must be established by the physician with parents as well as with child. Much patience is needed and play technique is helpful. The environment of the child, if unfavourable, should if possible be improved, and finally his unconscious attitudes should be gradually interpreted to him so that he becomes fully conscious of the reasons for his actions.

Lehman, E. (1944) *Amer. J. Dis. Child.*, 68, 190.

PSYCHONEUROSES AND PSYCHOTHERAPY

See also B.E.M.P., Vol. X, p. 232; and Cumulative Supplement, Key Nos. 1315–1317.

Psychoneuroses

Aetiology

Management of war neurosis.—Epstein discusses the aetiology, pathology and treatment of war neurosis. The first criterion in the definition of the condition is an absence of a psychoneurotic history and personality. Moreover, the experience of combat must be sufficiently intense to precipitate the neurosis. Other criteria include a rapid onset of irritability resembling a constant state of panic, and a relatively quick cure in the acute cases. Most patients do not break down until they have been exposed to a series of untoward experiences. These

include physical fatigue, loss of sleep, lack of food, exposure to danger, the death of comrades and narrow escapes from the enemy. The pathological mechanism consists of overaction of the sympathetic suprarenal apparatus and the conditioned reflex of fear. This results in dissociation between cortical activity and the subcortical emotional and vegetative functions. The characteristic symptom consists of the repeated re-enactments of the various threatening experiences that the patient has endured. Sleep is disturbed by terrifying nightmares. Fear and fatigue produce the physical signs of anxiety, but some patients are listless and apathetic. The patient is startled by sudden noises and immediately there develops a state of anxiety or of acute panic. The personality changes so that the patient becomes sullen and intolerant of others. A guilt reaction accompanied by emotional depression may occur in survivors of disasters. Careful training is of prophylactic value, for men are less likely to show fear reactions while they are performing duties that they know well. It is essential to begin treatment in the forward areas. The longer the treatment is delayed, the poorer the prognosis. Rest is obtained by the use of barbiturates to secure profound sleep. Psychotherapeutic measures include reassurance, exhortation, hypnosis and narco analysis, but deep analysis should be avoided because unconscious conflicts have no basic significance in war neurosis.

Psychopathology

Neuromuscular exhaustion—Nielsen describes 4 cases of neuromuscular exhaustion with atrophy and fascicular twitching, months were required for recovery. All the patients had greatly overworked themselves for a prolonged period, appearing oblivious of fatigue, until a final supreme effort resulted in exhaustion and paralysis. In one case, that of a schoolgirl 17 years of age, the patient starved herself in order to reduce her weight while she was practising strenuous gymnastic exercises. With extreme weakness there is psychomotor restlessness, the patient being unable to relax. Generalized muscular cramps and pains appear, the muscles later becoming flaccid with fascicular twitching. A sleep of exhaustion succeeds insomnia, and the patient awakes paralysed. In a few weeks atrophy appears with prominent fasciculation and there is severe loss of weight. Rest and good food produce gradual recovery but the patient never regains his former level, and focal atrophy of the most severely affected muscles—girdle muscles rather than the small limb muscles—remains. Temporary and residual neuronal changes may occur. After recovery, any overexertion causes a relapse, the patient being apparently "sensitive" to overwork as a victim of heatstroke is sensitive to heat. Patients also tend to be unaware of and to ignore the danger of overexertion. Nielsen considers that neuromuscular exhaustion must occur frequently in wars and famines, during great disasters many persons must succumb to it. The cases described were not seen until the later stages but the study of early cases might conduce to the discovery of rapid remedial measures.

Ocular symptoms of psychogenic origin—Oberndorf discusses ocular symptoms of psychogenic origin. Psycho analysis recognizes displacement mechanisms by which genital associations are switched to a secondary object. Such displacements or substitutions have their origin in constant repressions of instinctive urges (generally sexual), and may give rise to multiple physical symptoms including ocular disturbances such as blurred vision or blindness. In mythology the eye represents the sun and the eye of God, belief in the power of the evil eye is still prevalent. The eye is also a symbol of the female or male genital organs, in males the fear of blindness may represent the fear of castration as a deserved penalty of illicit sexual curiosity. Patients with neuroses not referable to their eyes often wear glasses, the author quotes the example of a patient who had always been a coward and who from boyhood had worn glasses in order to protect him from attack and to excite the sympathy of others. Glasses can become a symbol of lack of sexual attraction and both men and women may avoid their use so that they may not be thought to lack sexual vigour. Patients may report that at the time of prescribing glasses the ophthalmologist voiced his doubts whether they were the correct treatment, the patient in this case, however, will wear the glasses willingly because they give him an object to which to attach his neurosis. If on the other hand the neurosis can be cured, the ocular symptoms will disappear and the patient will equally willingly discard the glasses. The diagnosis of an ocular neurosis is extremely difficult and care must be taken not to confuse the symptoms with those which are due to an organic basis. Often it is wise not to inform the patient that his symptoms are psychogenic, when he has been told, however, that no organic basis for his symptoms are psychogenic, when applications should be discontinued.

Psychosomatic aspect of gastro intestinal disease—In a paper read at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, Vorhaus and Orgel discuss the psychosomatic approach to gastro-intestinal disease. It is becoming more and more recognized that the personality of a patient as a whole should be considered and treated, and not only the particular disease which he appears to have. For some time it has been known that the battles between psyche and soma are most frequently fought in the gastro-intestinal tract and that diseases in this region are either very largely functional (so called) in character or, if organic in origin are masked by psychological disturbances. After thorough physical examination has demonstrated the presence or absence of organic disease, the psychosomatic history should be taken. Adult emotional immaturity is the fundamental cause of psychosomatic illness, emotional instability causing conflict between the intellect and the emotions from which disharmony and consequent ill health result. By appropriate treatment of the individual the re-education of the emotions can be attempted. The patient should be given

time to tell his story in his own way, and the ideal method of examination appears to be casual conversation, utilizing free associations, and careful questioning. Patients suitable for psycho-analysis should be selected, and others, if sufficiently intelligent and flexible, should be given other appropriate forms of psychological treatment. Cases of combined organic and functional illness benefit by psychological as well as medical treatment. Psycho-analysts have found a constant similarity between the nature of the psychological conflict and the type of gastro-intestinal disorder, and the patient's emotional trends can be described in terms of three elemental tendencies applicable to both, namely (1) the wish to receive or to take as related to gastric disorders, (2) the wish to give or to eliminate as applied to cases of diarrhoea, and (3) the wish to retain as applied to cases of constipation.

The psychiatric casualty.—Overholser believes that the most important medical problem of the recent war was the prevention and treatment of psychiatric casualties. Mental and neurological disorders were responsible for the rejection of about 23 per cent of over three million recruits in the United States of America, and 32 per cent of those discharged from the Army were psychoneurotics. The recruit is faced with certain psychological hazards which include homesickness, strict regimentation, and loss of individuality, initiative and privacy. Warfare adds stresses caused by sudden fear, insomnia, mud, vermin and various diseases. On the other hand, the morale of military life is of particular value for the obsessive compulsive type of neurotic. Moreover, the prognosis of mental disorder among the Forces compares favourably with that in civil practice. Anxiety neurosis was commoner than the conversion hysteria and effort syndrome of World War I. The condition was generally attributed to some catastrophic event such as an explosion. The commonest psychosis was acute catatonic excitement occurring in patients with latent homosexuality. Treatment of the neuroses includes rest, occupational therapy and psychotherapy. Continuous narcosis facilitates rest in cases of profound exhaustion. Narco-analysis carried out by means of intravenous administration of sodium Amytal or Pentothal sodium (soluble thiopentone) is a method which releases inhibitions and enhances suggestibility. Shock treatments with insulin and electricity are drastic remedies but electric shock therapy is particularly useful for the depressions. Group discussions are valuable and a special form of discussion, the psychodrama, has also proved to be successful. Problems of the future involve questions of compensation and employment.

Clinical picture and classification

Ocular neurosis in the Royal Air Force.—Quoting Werner Bab's dictum that "the eye has to face, has to see, the whole of the hostility brought about by the struggle of, and for, daily life", Campbell and Cross describe ocular neurosis in members of the Royal Air Force and point out that most of the cases were those of chronic anxiety neuroses rather than of hysteria. They emphasize the fact that "the basis of a neurotic reaction is produced by any factor which induces an abnormal awareness of the ocular mechanism", citing as examples the child warned by a fussy mother not to strain his eyes; patients who have worn glasses at school and in whom when they are adult ocular neurotic symptoms develop; patients in whom diminution of visual acuity causes anxiety concerning the prognosis; the effects of heterophoria due to the strain of endeavouring to maintain binocular vision; persons with one blind or almost sightless eye who suffer great anxiety about the integrity of the normal eye; injudicious remarks by friends and ocular awareness instilled in the patient by blindness of a relative. The authors describe cases arising from psychiatric background, environment, domestic stress, head injuries and flying strain; they list the clinical manifestations as blindness or defective vision, asthenopia, photophobia and excessive blinking, night blindness and diplopia. The importance is noted of careful history taking and of detailed examination in order not only to exclude organic factors but also to assure the patient that a full investigation is being conducted. Two organic cases are cited, one of myasthenia gravis and one of thyrotoxicosis, both previously diagnosed as functional. Prognosis depends upon the basic personality of the patient and upon the nature and depth of the conflict involved. The authors emphasize that ocular neuroses are essentially polysymptomatic and further that symptoms tend to be contradictory and signs irregular. The importance is stressed of psychological investigation if the ophthalmologist is not a skilled psychiatrist.

Psychosomatic elements and neurosis.—Ewalt in discussing some psychosomatic problems divides them into two groups: (1) patients with symptoms referred to one of the physical systems but without evidence of pathological changes; (2) patients with marked structural alterations which in part may be due to psychological disturbances. The first group may be subdivided into (a) the psychoneurotics, (b) those in states of simple anxiety. The psychoneurotic patient, with a long-established and deep-seated maladjustment, can be treated satisfactorily only by a skilled psychotherapist. Under stress many individuals react with anxiety so prolonged and deep as to produce changes and symptoms in physiological function. Noting these the patient thinks he has a disease of the affected system. In the second large group, peptic ulcer, hypertension, coronary disease, bronchial asthma, mucous colitis and the arthritic disturbances have been specially studied. If psychological conflicts can produce structural alterations in the tissues it must be by alterations in autonomic and endocrine functions secondary to psychological disturbances; anatomically this means alterations in the cortical and hypothalamic regions. Can alterations in the autonomic physiology produce pathological organic lesions? Animal and clinical experiments show that organic lesions of

the central nervous system may produce ulceration of the gastro-intestinal mucosa. It has also been found that anxiety and hostility produce changes in the gastric mucosa. Such emotions are consistently found in patients with peptic ulcer who are often exaggeratedly aggressive, ambitious and independent, and the relief of such emotional states favourably affects the physical condition. Hypertension and heart disease have been similarly studied with encouraging but less clear results.

Trophic conditions—MacKenna discusses psychosomatic factors in skin disease and outlines a scheme based on suggestions made to him by Hodgson in 1943. Certain psychological trends can be linked up with some distinct skin affections. In hysterical persons, who use illness for the purpose of claiming sympathy or privileges, and in whom there may develop areas of complete or partial anaesthesia, a skin eruption may possibly be self-inflicted. In persons with obsessional trends, who are prone to skin infections and who are often highly intelligent, restless, tense and overconscientious, localized or general prurigenous, often lichenified, eruptions tend to develop. These persons are liable to neurodermatitis and to pruritus ani, and very apt to overtreat themselves and thus produce dermatitis medicamentosa. Anxiety types are liable to attacks of rosacea, which is often preceded physiologically by a loss of contractile power in the facial capillaries, and psychologically by long-continued social or sexual stress and anxieties. They have abnormal self-esteem combined with a guilt complex. Pompholyx of hands and feet may be caused by anxiety, which too may cause dysidrosis and the exacerbations of psoriasis, the last being linked with deep, repressed emotional factors. Narcissistic personalities suffer from a deep conviction of inadequacy and are often able to escape from insupportable positions by means of an intractable exudative skin eruption. In adults who suffer from impetigo, seborrhoeic dermatitis, and sometimes in those who have herpes zoster and acute eczema, a leper complex may be evident; they need to be reassured and to be kept from overtreating themselves because they feel unclean. If a carefully dated clinical history is taken from patients first and, after an interval, a carefully dated personal life history, and if phases of emotional and social difficulty, successes and failures are dealt with, interesting correlatives can often be found when the histories are compared. Emotional situations may thus be uncovered which may have precipitated physiological disturbances.

Psychotherapy

General treatment

Advantages possessed by the general practitioner—Gillespie discusses psychiatry in relation to general practice. Psychological disorders are common and neurotic patients today are tending to formulate their symptoms in psychological terms such as depression or fear, although physical diagnoses such as anaemia or debility still often serve as a cloak for underlying psychological disorder. In approaching the problem of psychiatry the general practitioner has certain definite advantages. Sometimes the question of terminology is thought to be difficult, but only about 6 names are necessary for classification. It is in psycho-analytical technique that the terminology becomes involved. Among the advantages possessed by the general practitioner are a knowledge of human nature and the power to practise suggestion. With regard to the latter, it is proper to mention the negative aspect of suggestion. The thoughtless labelling of a set of psychological symptoms with a physical diagnosis may fix the patient's anxiety along a line difficult to eradicate. The causes of psychological ill health may be classified as constitutional, situational and historical. In the first, the general practitioner often has advantages over the specialist. The specialist depends upon the giving of a true history by the patient without the concealment of essential facts, whereas the general practitioner has often a personal knowledge of the patient's family and past history which advantageously placed to assess the family background and the conditions of work. He may then explain the relation of the symptoms to emotional tension and state whether the situation must be endured or whether a change is advisable. In the third group, the historical causes, the general practitioner may be of help by supplying personal information. Gillespie states that in cases of psychological ill health due to sexual factors, the family doctor is often at a disadvantage through lack of knowledge of sexual pathology. Finally the author believes that psychoneurotic illnesses are among the most curable of chronic ailments and that psychiatry should attract the general practitioner since the approach to this branch of medicine is essentially clinical.

Barbiturates given intravenously—Lambert and Rees describe the results of intravenous barbiturate narcosis in the treatment of 126 cases out of a total of 247 consecutive cases of hysteria admitted to a unit of an Emergency Medical Service neurosis centre. In 19 cases verbal hypnosis was used and the remaining patients were treated by ordinary psychiatric methods. All patients received various kinds of occupational therapy. The barbiturates used—Sodium Amytal, 10 per cent solution, Pentothal (thiopentone) 2½ per cent solution, and Evipan (hexobarbitone) 10 per cent solution—except for the longer duration of action of the patient beforehand was found to be important and very slow and even injection of the drug used was essential. The most favourable state was the pre-anaesthetic phase of light narcosis, and conversation was kept up the whole time, the patient never being allowed to lose consciousness. Symptoms were usually readily removed by prior suggestion and per-

suasion and the patient was made to continue to use the recovered functions into the full waking state. It was found that intravenous barbiturate narcosis gave no better results than did ordinary persuasion and re-education, but the results were much more quickly obtained especially in cases of hysterical amnesia. The method was of little use in the treatment of somatic pains. The greater rapidity of effect was due partly to diminished inhibitions caused by the pharmacological action of the barbiturate and partly to the suggestive value of the procedure. Another, often unnoticed, aspect of this method is the increased confidence of the physician because of less embarrassment and the negligible risk of failure. The main disadvantage found was the precipitation in some cases of great motor restlessness, when the patients were restrained with difficulty from hurting themselves.

Psychotherapeutic methods

Shock therapy in psychoneurosis.—Kalinowsky, Barrera and Horwitz discuss the value of electric shock treatment in the psychoneuroses. Sixty-five selected cases of voluntary patients admitted to the New York Psychiatric Institute were treated with electric shock. The following types of psychoneurosis were represented: obsessive-compulsive, anxiety hysteria, conversion hysteria, mixed psychoneurosis and reactive depression. Many of the patients had been under observation for many months and most of them had had psychotherapy. In the obsessive-compulsive types a spurious improvement sometimes at first resulted, which disappeared after a few weeks. A few patients with severe symptoms became more amenable to psychotherapy and improved considerably under it. Patients with anxiety hysteria received little benefit from electric shock, and the results of treatment of conversion hysteria were similarly unsatisfactory. Several patients complained of being made worse. A small number who showed some improvement, either had asked for treatment because of improvement observed in others, or had a strong element of depression in the conversion syndrome. The best results were obtained in the so-called psychoneurotic depressives, the majority of such patients being benefited. Psychotherapy is advisable after shock treatment in these cases. Many complaints were made by patients, and some expressed fears of permanent memory impairment or of becoming insane. Improvement, if it occurs, comes slowly in neurotic patients, in contrast to the quick response—after the third or fourth convulsion—seen in some psychotics. It is much more difficult to decide the advisability of electric shock treatment for the neuroses than for the psychoses, and cases should be very carefully chosen. Anxiety neuroses and conversion hysterias should not be treated with shock, but psychoneurotic depressives can be treated with advantage if only for the purpose of clearing the depression. In general, however, the final results with neurotic patients are unsatisfactory, although fair results may be obtained in selected cases if the treatment is combined with psychotherapy.

General principles.—Katzenelbogen discusses the general principles of psychotherapy. The psychotherapist often has two problems to solve: first the patient's symptoms and secondly the problem of the patient's relationship to his surroundings. It is important to realize that sometimes successful treatment cannot be expected without change of environment. Psychotherapeutic procedures can be divided into two large classes. (1) Non-specific psychotherapy corresponding to symptomatic treatment in general medicine. This includes such processes as reassurance, persuasion, suggestion and hypnosis and has one absolute essential, a good rapport between psychotherapist and patient. The negative aspects of the above include the formation of iatrogenic diseases. (2) Specific or genetic-dynamic psychotherapy, implying a knowledge on the part of the psychotherapist of the cause of the illness and its mode of action. It is essential that the patient be made to recognize the causes and to experience them emotionally. In eliciting the causes the psychotherapist, if he believes that only those experiences which the patient has forgotten—particularly of childhood—are the essential factors, will use Freud's psycho-analysis or the free association technique as the method of choice. If, however, he considers that these experiences may occur in any phase of life he will choose to study the patient throughout life. In the type of psychotherapy which employs a study of the personality the taking of a comprehensive history is of primary importance. Since it is obvious that the patient will not wish to recount those experiences which he desires should remain in oblivion, it is essential that he be made to feel that he is an active partner in this form of therapy so that his interest will be aroused. Katzenelbogen concludes that such a history is the first step to take in the psychotherapeutic situation.

Campbell, A. M. G., and Cross, A. G. (1944) *Brit. J. Ophthal.*, 28, 394.

Epstein, S. H. (1944) *New Engl. J. Med.*, 231, 446.

Ewalt, J. R. (1944) *J. Amer. med. Ass.*, 126, 150.

Gillespie, R. D. (1944) *Brit. med. J.*, 2, 263.

Kalinowsky, L. B., Barrera, S. E., and Horwitz, W. A. (1944) *Arch. Neurol. Psychiat.*, Chicago, 52, 498.

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MacKenna, R. M. B. (1944) *Lancet*, 2, 679.

Nielsen, J. M. (1944) *J. Amer. med. Ass.*, 126, 801.

Oberndorf, C. P. (1944) *Arch. Ophthal.*, N.Y., 32, 443.

Overholser, W. (1944) *New Engl. J. Med.*, 231, 377.

Vorhaus, M. G., and Orgel, S. Z. (1944) *J. Amer. med. Ass.*, 126, 225.

showed diminished creatinine. Blood investigations were necessarily limited in extent; from the results obtained only non-protein nitrogen showed any variation in relation to the mental cycle. The greatest values occurred on the day prior to the transition from depression to mania. The blood sugar, plasma chloride, serum calcium, total phosphates, erythrocytes, haematocrit and haemoglobin were within normal limits and exhibited no periodic fluctuations.

Klein, R., and Nunn, R. F. (1945) *J. ment. Sci.*, **91**, 79.

PSYCHOSES: SCHIZOPHRENIA

See also B.E.M.P., Vol. X, p. 302; and Cumulative Supplement, Key No. 1321.

Aetiology

Basal metabolism

Experiments on hippuric acid synthesis.—Michael, Looney and Borkovic discuss experiments on hippuric acid synthesis in dementia praecox. Hippuric acid is synthesized from benzoic acid by a mechanism of detoxication performed mainly by the liver. Studies were made on 18 male schizophrenic patients, including catatonic types, and on 9 male controls. To the subjects, fasting and at rest, 18 milligrams of sodium benzoate per kilogram of body weight were administered orally. Four samples of urine were then taken at hourly intervals. Both groups detoxicated approximately 75 per cent of the ingested sodium benzoate. Four of the patients showed initial retardation in the rate of synthesis and 2 excreted unusually large amounts during the first hour of synthesis. Three patients synthesized amounts considerably less than the lowest value for the controls and 3 exceeded the range of the controls. Retention of uric acid after ingestion of sodium benzoate was slightly greater in the patient group. During the synthesis of hippuric acid there were changes in the level of pyruvic acid in the blood correlated with the intensity of the synthesis. In this study corrections for body weight were made, otherwise the control group apparently would have synthesized more hippuric acid than would have the patient group. It is shown that the majority of schizophrenic patients, including catatonic types, have adequate ability to detoxify benzoic acid. One-third of the number of patients showed some irregularity in the onset of synthesis of hippuric acid. The differences in uric acid retention in the two groups and the shift in the pyruvic acid level in the blood cannot be adequately interpreted.

Clinical picture

Biopsy findings in the testis

Hemphill, Reiss and Taylor describe the histological biopsy findings in the testis in schizophrenia and other mental disorders. The clinical correlations and implications of those findings are described by Hemphill in another paper. The specimens were taken from 90 cases of schizophrenia and 25 cases of other psychoses. All the patients except 3 were well nourished, in good bodily health and on standard diet, and there was little possibility of vitamin deficiency. No schizophrenic was accepted who had gross gonadal defects, such as obvious hydrocele or incompletely descended testis. The histological material was classified in five grades: (1) complete normality, (2) normality with slight defects, (3) moderate atrophy, (4) and (5) severe and very severe atrophy with, in the worst cases, complete loss of function. It was found that the testicular changes in schizophrenia varied between a slight reduction in spermatogenesis and gross atrophy, the latter—consisting of hyalinization of the basement membrane with arrest of spermatogenesis causing progressive degeneration of the seminiferous epithelium and final destruction of the tubule—being found in more than half the number of cases. Chronic systemic infections, local trauma and toxic processes cause interstitial fibrosis, with degenerative atrophy but not hyalinization. The changes found in the biopsies from patients with non-schizophrenic psychoses and mental defect, were all within normal limits, if age and one or two cases of organic disease were allowed for. The atrophy in schizophrenia is an integral part of the psychosis and varies with its malignancy. Every degree of atrophy was found in a series of early cases of less than one year's duration. The atrophy may appear before the mental defect does and is therefore of diagnostic value. The severity of the atrophy is not related to age—except that very malignant schizophrenia often starts in early life—nor was any correlation found between the physical type or the family history of insanity and the condition of the testis. Moderate atrophy was found in mild arrested schizophrenia, but there was no significant change in the paranoid form. The internal secretion of the testis did not appear to be affected in most cases and no relation was found between the excretion of the 17-ketosteroids and the degree of atrophy. The testis disorder is a sign of a complex central imbalance, and it is suggested that an endocrine imbalance with relative and qualitative gonadotrophic failure is responsible for the atrophy and, in a susceptible constitution, for the schizophrenia.

Treatment

Specific

Electrical convulsion therapy and the cerebrospinal fluid.—Maddux, Aldrich and Blair discuss the effect of electrical convulsion therapy on the cerebrospinal fluid. The patients were young men who had recently been discharged from the Forces with the diagnosis of schizophrenia. A constant time interval of 0.1 second was used and the voltage was raised to the convulsive threshold, sometimes to 250 volts, producing a current between the electrodes of 700-900

milliamperes This is somewhat higher than the current used by most other workers. A lumbar puncture was performed on each patient prior to treatment. The operation was repeated 24 hours after a seizure. In order to investigate the possibility of a cumulative effect the second lumbar puncture was performed after a different number of seizures in each case. The procedure was controlled by similar tests on patients who did not have convulsion treatment. The examinations proved that there were essentially no changes in the average cerebrospinal fluid constituents after 1-10 electrical convulsion treatments. The pressures, cell counts, and the amount of sugar and total protein were within normal limits. All benzidine and Pandey tests were negative. Rathnell has reported the development of a meningitic type of colloidal gold curve after metrazol (leptazol) therapy, but Maddux, Aldrich and Blair found that the colloidal gold curves were normal after electrical convulsion treatment. No significant individual differences were noted with respect to the interval between the examinations, the age of the patients, the clinical manifestations of the psychosis, and the ultimate success or failure of the treatment.

Serum gonadotrophin—Atrophy of seminiferous epithelium and failure of spermatogenesis are known to occur in schizophrenia. Hemphill and Reiss have treated cases with gonadotrophic hormone of pregnant mare's serum on the basis of histological findings in testicular biopsy specimens. Gestyl was administered in 800-1,000 unit doses daily for variable periods up to 48 days. The effects of intensive treatment on the mental state and gonad function in a selected series of 18 male schizophrenics are discussed. Two had a symptom free remission, in one of these there was a relapse after a year, and the patient was again treated and had a further remission. Some distinct mental change with more bodily activity occurred in 6, change for the worse with great increase in sexual behaviour in 4, and no mental change at all in 6 cases. Change was observed in the histological picture of the testis: thinning and dehyalinization of the previously thickened basement membrane and increased activity in the seminiferous epithelium and Sertoli cells. There was, however, no evidence of an increase in mature sperm production. In 4 similarly treated female cases of chronic schizophrenia with amenorrhoea, 1 patient was discharged from hospital and 2 improved. In all 3 menses were restored. The fourth case failed to respond. The authors point out that nearly all the cases were long-standing, with a very poor prognosis. Other attempts at treatment, for example by convulsion therapy, had failed to produce any mental improvement. Hemphill and Reiss believe that there is a clear justification for hormone therapy in schizophrenia, but the therapy must be based on proper diagnostic indications. Post mortem studies suggest that in many cases there is a pluriglandular hypofunction and that it would be well worth while to treat a series of cases early in the development of the psychosis with a combination of other anterior pituitary as well as gonadotrophic hormones.

Anaesthesia in prefrontal leucotomy—Lee discusses anaesthesia in prefrontal leucotomy. General anaesthesia is usually the method of choice, but an explosive mixture must not be used in case diathermy should be necessary. Ether increases oozing and chloroform may increase the risk of ventricular fibrillation when adrenaline is used to lessen bleeding. Gas oxygen with minimal Trilene (trichlorethylene) is a suitable anaesthetic but occasionally produces tachypnoea and cardiac arrhythmia and there is more postoperative vomiting than when Pentothal is used. In a series of 75 cases the favourite method of general anaesthesia, (hyoscine) $\frac{1}{16}$ grain were given an hour before operation. Omnipon $\frac{1}{2}$ grain and scopolamine 2 fluid drachms of paraldehyde by the mouth. Fauces, larynx and nares were sprayed with 2 per cent amethocaine hydrochloride and an intravenous injection of Pentothal Sodium secured to the arm by rubber tubing and artery forceps. Gas and oxygen was administered through a Magill intratracheal tube, lubricated with Brennan's 10 per cent Nupercaine paste, must be used, the patient's colour being kept pink all the time, and not less than 25 per cent oxygen minute of the total gases must be kept running in order to prevent accumulation of excessive amounts of carbon dioxide. A three way tap should be interposed between the syringe and the intravenous needle, so that saline can be dripped through to maintain potency of the critical stage of the operation, when the brain tissue is divided, and 0.1 gramme may be given immediately before the division is carried out. In the above series of cases the average dose of Pentothal was 1.1 grammes and the average operating time was 55 minutes. Trilene may be used in order to control an excessive laryngeal reflex. Blood pressure and pulse rate should be charted every 5 minutes, a gradual drop of the former occurs during the operation.

Unsuccessful use of blood transfusion therapy—Pfeiffer and Pescor record an experiment in order to determine the value of the treatment of schizophrenia by replacing the patient's blood by that of normal donors. The structure of the brain cells being unaffected, schizophrenia may be caused by their faulty metabolism, either because of lack of certain essential substances or because of the presence of toxic products which interfere with metabolism. Pescor noted the resemblance of certain symptoms of schizophrenia to those of anoxaemia in normal persons. The fault in the former, however, is one of the utilization rather than of the lack of oxygen in the brain cells, perhaps through the absence of an essential enzyme or the presence of an anti-enzyme. Schizophrenics have been found to have in their blood a

different glutathione content from that in normal persons, and the possibility of the suspension of cerebral oxidation by the depletion or destruction of certain substances in the blood has been investigated with some success. Six patients with varying types of schizophrenia of from 9 to 18 months' duration were given from 3 to 7 transfusions within 7-10 days. The total blood in each case removed varied from 2.50 to 6.10 litres, and the blood replaced from 2.25 to 7 litres. The donors were non-psychotic patients from the Public Health Service Hospital at Lexington, Kentucky, and were of the same blood group as the recipients, with one exception in which a group B patient had as his last donor one in group O. Improvement did not result in any case except that of one patient in whom complete remission of the disease in 4 weeks could have been accounted for by other factors.

Hemphill, R. E., and Reiss, M. (1945) *J. ment. Sci.*, **91**, 1.

— and Taylor, A. L. (1944) *J. ment. Sci.*, **90**, 681, 696.

Lee, J. A. (1945) *Brit. J. Anaesth.*, **19**, 101.

Maddux, J. F., Aldrich, C. K., and Blair, Joyce J. (1945) *J. nerv. ment. Dis.*, **101**, 330.

Michael, S. T., Looney, J. M., and Borkovic, E. J. (1944) *Arch. Neurol. Psychiat., Chicago*, **52**, 57.

Pfeffer, A. Z., and Pescor, M. J. (1944) *Arch. Neurol. Psychiat., Chicago*, **52**, 131.

PSYCHOSES: PRE-SENILE AND SENILE PSYCHOSES

See also B.E.M.P., Vol. X, p. 342.

Senile psychoses

Dementia

Results of mental tests.—Halstead describes the results of mental tests given to 18 demented senile patients and compares these results with those of a previous group (A) of 20 patients of similar ages and less advanced dementia. Both group (A) and group (B) had little difficulty in Recognizing Photographs, Naming Months, and Packing Cubes in Box, while Knox Cubes, Porteous Mazes, Tapping and Recall of Paragraph were difficult for all. Group (B) found relatively more difficulty in Reversing Months, Repeating Digits Forward, Recalling a Paragraph, Naming Colours in Reverse, Arithmetic, and Porteous Mazes. The average mental age shown by this group on 13 of the tests was 6.8; the highest, - 10.5, was on the Vocabulary Test, and there was a gap of 5.5 years between this and the worst tests. The average demented senile was therefore at about the mental level of a child of 7 years of age. On the full scale of 25 tests the median of group (A) was 13.77 ± 6.39 and that of group (B), 23.58 ± 5.73 , out of 38 ranks. The average percentage of failures on the tests was 22 per cent in group (B) and only 5 per cent in group (A). Group (B) showed a steep drop in mean scores with increasing age, and total production was much greater in group (A). The score profiles of all the patients showed little in common and there was very little difference in "scatter". The investigation brought out points worth following up in other cases of organic impairment. The rapid decline of recent memory generally and of substance memory particularly, was shown, and the tests could be ranked in order of difficulty so as to bring out the different rates of decline. No short cut was found to assessment of deterioration but a variety of tests had to be used in order to find out the patients' strong and weak points. Special attention should be paid to these tests which are found to be difficult for most patients with organic impairment.

Halstead, H. (1944) *J. ment. Sci.*, **90**, 720.

PSYCHOSES: GENERAL

Treatment

Specific

Cases suitable for electric shock treatment.—Gold and Chiarello describe the result of a study of 121 consecutive male patients who were treated with electric shock at the Brooklyn State Hospital. The study was undertaken in order to determine the prognostic value of certain clinical features so that a scientific selection of cases suitable for electric shock treatment could be made. The patients were classified after treatment as "much improved", "improved", "improved in behaviour", and "no change". The first category, "much improved", might rather be called "recovered". It was found that the following symptoms at the onset of the illness were of good prognosis: muteness, perplexity and confusion, fear of an immediate personal threat or danger, depression and suicidal intent. Favourable features, too, were within the age groups 51-60 and 11-20 years, a stable family history, short duration of illness—preferably not more than 3 months and certainly not more than a year—sudden onset due to an exogenic precipitating cause, good school and work record, satisfactory marital and sexual relationships and a friendly personality. A poor prognosis was given for patients showing gradual onset of illness—lasting for more than a year—previous shock therapy, gradual loss of interest, negativism, restlessness, ideas of reference, grandiose delusions and a withdrawn and inhibited personality, or with other personality traits such as chronic alcoholism, stuttering, severe outbursts of temper, and history of hypochondriasis. It was considered to be important to make a complete psychiatric examination before treatment with electric shock, and to follow carefully the patients' mental reactions.

Curare-protected convulsion shock.—Woolley describes the findings of a detailed study of blood pressure, pulse and respiration made on patients in the Sheppard & Enoch Pratt

Hospital, Towson, Maryland, who were treated with curare protected convulsion shock. The curare used was intocostrin, a stable preparation from unauthenticated curare, standardized and uniform in action, containing little or no cardiac depressing factor. The data studied consisted of 52 pulse, respiration and blood pressure curves with curare alone, more than 700 studies of pulse and respiration with curare and then shock, and 98 studies of blood pressure with curare followed by metrazol (leptazol) or electric shock. Great variety was found in circulation and respiration of different individuals, and in the same individual at different times. Anticipation of treatment tended to keep the blood pressure up in spite of administration of curare. The respiratory effects of curare were stridor, due either to weakness of the chest muscles or spasm of the bronchioles, and general weakness of respiratory muscles. Convulsion shock, metrazol or electric, caused manifest interference with respiration, considerable variation in blood pressure, sometimes of extreme degree during and after the seizure and similar results on pulse rate, regularity and quality. The rapid changes of blood pressure in the clonic phase must play an important part in any brain damage which results from the convulsions. Muscular contraction is not the only cause of blood pressure changes since they occur in the post seizure phase. Extreme falls of blood pressure, pulse or respiration are overcome by administration of Prostigmin or adrenaline, suggesting that curare is an important factor. Woolley considers that the great blood pressure changes play a larger part in causing the post-convulsion confusion and memory defect than has been hitherto recognized. It had not been found possible to study the effect of convulsion shock without curare but it was considered that the respiratory effects would be less and that the blood pressure effects might be greater if curare were not used.

Shock therapy

Methods in review—Ruskin reviews the history of shock therapy of the psychoses which is an old therapy now revised by the use of electric shock. The modern method of producing this, the employment of a standard type of sinusoidal shock apparatus, is described. Treatment usually is begun by use of a current of 400 milliampers for 0.3-0.5 second. If a convulsion is not obtained the length of time and the strength of current may be increased until a convulsion results. Various theories have been advanced to explain the effectiveness of shock therapy. When emotional conflicts interfere with normal behaviour, lower centres of control assert themselves and the individual's behaviour is no longer fully integrated. A vicious circle arises, as abnormal emotional reactions, originating from the autonomic nervous system, over which the cortex has no direct control, accentuate the newly acquired abnormal mental behaviour. Shock therapy may in some unexplained way dislodge psychotic symptoms. Various factors such as fear and guilt probably operate in different cases, depending upon the individual reaction type. All forms of pharmacologic and electric shock therapy cause powerful stimulation of the autonomic nervous system, followed by depression or temporary inhibition of the higher cerebral centres. The least drastic method is the administration of a subconvulsive faradic current, immediately followed by short Pentothal anaesthesia. The patient's subsequent relaxation is obtained under better control than is possible with the other methods. The relative efficacy of the different types of shock therapy is not completely established but the results of electric shock, the most easily administered and least expensive method, are comparable to those of insulin and of metrazol (leptazol) shock. The best response is obtained when the personality is acutely involved and when the psychotic symptoms are decidedly unpleasant to the patient, as in psychoses accompanied by an element of guilt with depression. The author states that all forms of shock treatment should be considered merely as adjuvants to psychotherapy.

Rest

Rest can be a dangerous remedy—Menninger states that the concept of rest as a form of treatment in psychiatry arose from neglect of the consideration of psychological factors. It is a fallacy to suppose that the lessening of muscular activity will cure psychological symptoms. The neuroses, psychoses and maladjustments in a patient are the result of misdirected rather than of insufficient energy. Modern treatment attempts to redirect wasted energy and to balance creative and destructive activity. The patient who for any reason is unable to maintain this balance carries on with his task with increasing difficulty and inefficiency. The work cure, according to which the individual is driven to more strenuous efforts, is no more sound than is the rest cure. The modern psychiatric hospital seeks to enable the patient to find an outlet for his instinctive urges in work and play properly taught, selected, graded and expanded. Aggressive tendencies turn inwards if they are not turned outwards by physiological, mechanical and psychological devices. Failure to turn such tendencies outwards means that the patient's aggressive energies will become self destructive. Rest can be a dangerous remedy, but nevertheless the psychiatrically disturbed patient who cannot work or play efficiently, usually cannot rest adequately either, and steps have to be taken to improve this capacity by the use of selected sedatives, hydrotherapy, prolonged immersion baths and the like. Prompt and complete rest may be of enormous benefit to the psychiatric syndromes that emerge in combat troops, airmen and shipwrecked sailors who have been exposed to prodigious physical and mental stress.

Gold, L., and Chiarello, C. J. (1944) *J. nerv. ment. Dis.*, 100, 577.
Menninger, K. (1944) *J. Amer. med. Ass.*, 125, 1087.

Ruskin, S. H. (1945) *Arch. phys. Med.*, **26**, 168.
 Woolley, L. F. (1944) *J. nerv. ment. Dis.*, **100**, 1.

PUERPERIUM

See also B.E.M.P., Vol. X, p. 365; and Cumulative Supplement, Key Nos. 1326–1329.
Management of the normal puerperium

Posture

Details of postural treatment after childbirth.—Rotstein decided to curtail the postpartum period of rest in 150 cases, but no patient was included who had any complication of pregnancy. Each patient was encouraged to move about in bed immediately after delivery and to lie on the abdomen for one hour on the third day. On the morning of the third or fourth day, if the 4-hourly temperature had not been above 99.6° F. for the preceding 24 hours, the patient was permitted to sit in a chair for 2 hours. This was repeated in the afternoon. On the fifth morning the patient was allowed to walk about. With this routine the women felt much stronger than did those kept in bed for the usual 10 or 12 days. Involution of the uterus was accelerated and uterine prolapse did not ensue. There were not any cases of thrombophlebitis and delay did not occur in the healing of episiotomy wounds. The morbidity rate was not increased. On the patient's first day out of bed the initial bleeding was more profuse than usual. On the day of discharge, however, which varied from the sixth to the eighth day, the lochia in 60 per cent of the cases was almost serous.

Complications other than sepsis

Stress incontinence

Details of remedial operation.—Macky has devised an operation to cure stress incontinence due to the trauma of labour, a condition which may not be manifest for months or years after confinement. At the commencement of the operation the bladder must be empty and, as far as is possible, free from infection. The bladder is exposed by a suprapubic incision and the bladder wall is incised vertically. A suction nozzle is inserted through a small incision in the vesical mucous membrane in order to remove any urine that may have collected. The sucker is removed and two ounces of acriflavine solution are poured into the bladder. The incision is extended to a total of 2 inches. A Harris retractor is inserted and the bladder neck is inspected. A small incision is made on the outer side of the veins which proceed from the region of the ureteric orifices along the lateral borders of the trigone. The incision is deepened and a Harris model of Young's boomerang needle is passed from one side to the other so that a catgut thread is drawn under the trigone slightly above the middle of its extent. The thread, held in forceps, serves as a tractor. The incisions are lengthened and the apical portion of the trigone is dissected from its bed. Dissection laterally discloses the remains of the internal sphincter. A mattress suture is passed through the tunnel under the dissected portion of the trigone to include some sound muscle on each side. When this is tied the severed ends of the torn sphincter are drawn into the original position beneath the trigone. In order to avoid strain on the repaired sphincter, suprapubic drainage is provided for 3 weeks. The catheter is plugged prior to removal and voidance of urine becomes normal. The patient is allowed up the next day and is discharged from hospital at the end of the fourth week.

Macky, F. (1944) *J. Urol.*, **52**, 27.

Rotstein, M. L. (1944) *J. Amer. med. Ass.*, **125**, 838.

PYELITIS

See also B.E.M.P., Vol. X, p. 404; and Cumulative Supplement, Key Nos. 1330–1332.

Clinical picture

Chronic type

Sterile pyuria and tuberculosis.—Since 1935 some 16 articles have appeared in the literature on sterile pyuria. According to Briggs this shows that the condition is becoming recognized as a clinical entity. The evidence points to a Gram positive coccus against which the sulphonamide drugs are useless as the likely organism. The signs and symptoms strongly suggest renal or genito-urinary tuberculosis and it is recommended that in the absence of proof of the tubercle bacillus or on the strength of pyelographic evidence arsenical drugs may be used after less toxic ones have failed. Briggs gives 4 case reports in detail. (1) A man aged 74 years complained of frequency, dysuria and pain in the glans penis. Analysis of the urine showed albumin and pus but no bacteria on smear or culture. After several small doses of neoarsphenamine the condition greatly improved and the symptoms disappeared. The urine then showed many Gram positive cocci but this was not considered to invalidate the diagnosis. (2) A man aged 35 years had frequency, dysuria, tenesmus and haematuria. Urine analysis showed there to be albumin and pus but no bacteria in the stained sediment; a pyelogram showed normal kidneys. The patient was given 3 doses of 0.3 gramme of neoarsphenamine at 4-day intervals. He reported 5 years later that he had had no further trouble. (3) A woman aged 22 years complained of pain in the right lower side of the back, frequency, dysuria and tenesmus. Albumin and pus were found in the urine but no bacteria were found on smear or culture. The patient was given 4 intravenous doses of neoarsphenamine and had immediate relief. (4) A man aged 33 years had frequency, tenesmus, urgency and haematuria. Urine analysis showed the presence of albumin and pus; there were not any bacteria and culture

a rise in *OX Proteus* 19 titre to fourfold or more should occur before a diagnosis of typhus fever is accepted. The Weil-Felix reaction is simpler than are determinations of rickettsial agglutination. With appropriate antigens, the complement fixation test is applicable to psittacosis, choriomeningitis virus infections and influenza and to some cases of atypical pneumonia. Heterologous antibodies are useful in the Paul-Bunnell reaction in glandular fever and the cold erythrocyte agglutination test for atypical pneumonia. Blood culture is of great assistance in enteric fever and is often positive later in the disease than is usually appreciated.

Stuart-Harris, C. H. (1945) *Practitioner*, 154, 99.

RADIOLOGY IN DIAGNOSIS AND TREATMENT

See also B.E.M.P., Vol. X, p. 456; and Cumulative Supplement, Key Nos. 1340-1343.

Methods of radiography

Venography

Use of Diodrast.—Baker and Miller record further experiences with venography, using Diodrast (diodone) by direct venepuncture as a contrast medium and making serial exposures of the whole of the leg and thigh during the period of injection. They are able to demonstrate clearly the site, and very often the extent, of a venous block. In acute superficial block the dye stops abruptly at a connecting vessel and turns towards the deep circulation or another area of the superficial plexus. This is the pattern most easily demonstrated in acute superficial block but a second pattern is sometimes seen of short lengths of straight non-dilated veins fading out into the tissues. In chronic superficial block the veins are dilated and tortuous and of uneven calibre. Tortuosity and increase in lumen are typical of chronic disease whether in the superficial or the deep circulation. In all of 11 cases of acute deep block studied there was distinct evidence of acute block in the superficial veins as well—confirmation of the theory that deep acute phlebitis originates in the superficial circulation. The veins cannot be seen in either acute or chronic deep block, but in acute deep block the superficial circulation resembles that seen in acute superficial block. The demonstration of chronic deep block by venogram when deep circulation appears to exist on clinical examination, will save much aggravating surgical interference. In external iliac block, the dye follows the pudendal circulation into veins of the lower abdominal wall, or comes out in the pudendal circulation of the opposite side, or passes back by the pudendal circulation into the pelvis. In one case the dye passed back into the patient's thigh and did not enter the pudendal circulation. Tilting of the table to 15 degrees from the horizontal in order to raise or lower the head did not affect the speed of the dye's passage.

Systematic radio-diagnosis

Alimentary tract

Cholecystography in diagnosis of gallbladder disease.—Sosman discusses cholecystography in the diagnosis of gallbladder disease. Attention to detail and a rigid precise technique are necessary for accuracy of diagnosis. Good fast apparatus should be used—the better the film and the technique generally, the more accurate the diagnosis. The usual procedure is to give 3.5 grammes of sodium tetraiodophenolphthalein (iodophthalein) after a fat-free evening meal, or 3 grammes of Priodax, which gives less reaction and little, if any, opaque residue in the bowel. After location of the gallbladder shadow three films, with slight variation in rotation, should be taken, one at least at the end of expiration. The patient is given a fat meal, and 2 hours later two more films are taken, using the same position and technique. The facts demonstrated by cholecystography are the size, shape and position of the gallbladder, the amount of filling and the relative concentration, the presence or absence of calculi and the amount of emptying. The size, shape and position are very variable. Situs inversus should be kept in mind. Changes in shape may indicate fixation or adhesions by extrinsic disease. If there is no visualization of the gallbladder by opaque material the correct interpretation is a non-functioning gallbladder. In 90 per cent of such cases gallstones have been found at operation, and the accuracy of this finding alone is nearly 99 per cent for grossly pathological gallbladders. There may be normal function and a normal cholecystographic shadow with chronic or even acute cholecystitis. Gas in the colon or the descending duodenum is the greatest source of error, and motion due to breathing is another frequent cause. Overlapping shadows or papillomata and adenomata may simulate gallstones. Rarely the gallbladder may be congenitally absent.

Radiology of the appendix.—In an address on some problems of appendix radiology Rackow points out that owing to its anatomical position radiological examination of the appendix cannot be carried out with the same precision as it can in the rest of the alimentary canal. By the time barium has reached so far, in the case of the test meal, it has become diluted and dispersed; with barium enemas filling is capricious. It is argued that if the appendix retains barium for some time this cannot be regarded as due to inability to contract, since contraction must have taken place in order to allow of expulsion of faecal contents and of their replacement by barium. A normally healthy appendix may take some time to expel barium which tends to become dehydrated and caked, and so to form concretions. It is possible that a normal appendix may not contract during 24 hours, and it is submitted that an appendix which shows no barium retention after palpation for some minutes has not yet accepted any. If attempts are made to encourage appendicular activity by administration of

magnesium sulphate it may happen that the caecum and appendix have expelled all the barium before examination, and experience is that if there is not any barium in the caecum there will not be any in the appendix. The author finds that he gets a much higher percentage of barium fillings if he gives 2 barium meals at an interval of 12 hours, and 2 drachms of magnesium sulphate 2 hours after the first meal.

Skiagraphical diagnosis of pancreatic disease—Poppel and Marshak review the skiagraphical diagnosis of pancreatic disease. Apart from direct observation of dense masses, calcifications, opaque foreign bodies or collections of gas with fluid levels in the upright or lateral recumbent postures, the criteria of pancreatic disease depend almost entirely upon the presence of a pressure defect. The manifestations are therefore not pathognomonic for any single lesion. The larger the mass and the nearer it is to the contrast filled stomach or bowel, the easier will be its detection. Disease in or around the pancreas which does not enlarge it or the regional lymphatic glands is impossible to diagnose skiagraphically. Among signs which point to a mass in the region of the head of the pancreas are enlargement, displacement, fixation or spreading out of the duodenal loop and diminished calibre of the duodenal lumen. Poppel and Marshak also describe a pressure defect on the outer wall of the descending duodenum due to a distended common bile duct, and the failure in filling of the lower portion of the duct which is seen after cholangiography in cases in which there is a mass in the pancreatic head. Masses in the body or tail of the organ may cause displacement of the stomach and indentations of its curvatures, but the signs are greatly influenced by the body habitus. Displacement of the mid-transverse colon and of the ascending duodenum are also noted. Intrapancratic masses can be simulated by enlargement of the regional lymphatic glands, abdominal aneurysm, omental cysts, diaphragmatic hernia and new growths in the stomach wall.

Circulatory system

Intravenous injections of fluorescein—Lange and Boyd state that intravenous injections of fluorescein can be made visible by irradiating the blood vessels of the skin and mucous membrane with a beam of long wave ultra violet light. The staining, however, is obscured by pigmentation. Photo-electric examination with the Dermofluorometer is used in testing capillary permeability and the circulation time. Diffusion of the dye can easily be observed under the capillary microscope. The method is employed in the diagnosis of peripheral vascular disease since the staining is reduced by an impaired circulation. Hyperfluorescence occurs in the presence of inflammatory lesions such as thrombophlebitis of the superficial vessels, but venous congestion and vasospastic disorders cause diminished staining. In over 1,000 patients injections of fluorescein caused no toxic effects apart from 11 instances of vomiting or retching. The test was used in 9 cases of acute embolism of the lower extremities. In 7 cases the exact level of the cutaneous blood supply was shown by a sharp line of demarcation at the point at which normal fluorescence stopped. This established with certainty the lowest possible level for amputation. In 2 patients it was demonstrated that the embolus had not produced complete vascular occlusion, for fluorescence was observed at the tips of the toes. Two types of peripheral gangrene were found to be associated with arteriosclerosis. The more common type involved the larger vessels. The fluorescence of the entire limb was greatly diminished and amputations at high levels were necessary. There was a better prognosis in the second type of gangrene, in which occlusion of the smaller arteries caused a slight decrease in the amount of staining. The diagnosis of thrombo angitis obliterans was confirmed by the combination of good fluorescence with greatly reduced oscillometric values. Ulcers due to varicose veins stained poorly, but the bases of syphilitic ulcers were fully fluorescent.

Female genital tract

Hysterosalpingography—Bernstein describes hysterosalpingography with Viscorayopake, a new non toxic opaque medium. Stereoptical technique in hystero-radiography facilitated diagnosis. The procedure is suitable for consulting room use since patients are usually ambulatory 15 minutes after its termination. Transitory nausea and vomiting were observed in a few of the 52 patients who were investigated. Thirty two made no complaint during or after the injection but 15 complained of discomfort or mild pain and 5 had severe pain. Mild sedation before the test is advisable for apprehensive patients. Contra indications are acute pelvic disease, gonorrhoea, ectopic or intra uterine pregnancy, cervical carcinoma or infection, and epilepsy. In 2 cases of the last named condition a *petit mal* syndrome occurred during investigation. The test should not be performed until after the menstrual or ovulatory phase, or for 6 months *post partum*, or during 30 days after operation. Investigation of abnormal bleeding should be undertaken only during the phase of recession of active bleeding. In 38 women who were investigated by hysterosalpingography after Rubin's test (transuterine insufflation with carbon dioxide) had been performed the findings agreed in all but one, in whose case the former revealed patency when insufflation had indicated tubal closure. In another case hystero-radiograms disproved cornual obstruction which had been observed in previous x ray films. A physiological contraction of the uterotubal sphincter is suggested in explanation. The importance of hysterosalpingography in investigation of sterility is emphasized. It demonstrated distinct curling, dilatation and partial obstruction, probably due to adhesions, in patent tubes. Infantile uterus, incomplete fusion of Müllerian ducts, a cervix 4 inches in length, bicornute uterus and ovarian cyst were all diagnosed radiographically. In 14 other cases diagnosis was amplified and in some, surgical plans were modified. The procedure was

unwittingly performed in 3 gravid women, all of whom, however, went to term. All showed cornual closure, suggesting that pregnancy may produce or coexist with physiological contraction of uterotubal muscle.

Norment describes the use of Viscorayopake, a new contrast medium, in visualizing the interior of the female generative tract. Iodized oils, hitherto the only available radio-opaque substances, are unsuitable for routine use since they are very slowly absorbed and cause a foreign body reaction, which may eventually bring about a tubal constriction. Viscorayopake, containing an organic iodine compound combined with a polymeric form of polyvinyl alcohol which renders it viscous, is rapidly absorbed and relatively non-toxic. With small, shallow uterine cavities, the dye is best instilled under low pressure through a de Pezzer catheter, previously inserted through the cervical canal and pulled down against the internal os in order to prevent leakage. The catheter is clamped while skiagrams are taken, and is then immediately unclamped. For larger uterine cavities, a small rubber balloon is inserted, then Viscorayopake is instilled. In each of some 20 patients having various gynaecological complaints, hysterosalpingography by this method gave clear sharp outlines. No reactions occurred and there was rarely any evidence of the contrast medium in films taken one hour after Viscorayopake was allowed to drain from the internal genitalia. Five case reports illustrate the use of the dye in demonstrating the presence or absence of tubal obstruction and in determining whether uterine bleeding is of organic or of endocrine origin. It is also useful as an aid in the diagnosis of disease of the uterine adnexa. Norment claims that hysterosalpingography is essential to the intelligent management of patients suspected of having uterine or tubal obstruction, and that this is now practicable as a routine procedure in gynaecological examinations. The patient can usually be ambulatory.

Nervous system

Myelography with Abrodil.—Arnell describes his experiences with Abrodil for myelography of the lumbar region in cases of suspected herniation of discs. Abrodil, introduced in 1931, is a water-soluble substitute for the iodized oils, the use of which had often been followed by chronic arachnoiditis. Abrodil is generally considered to be comparatively non-irritating and the reactions—some of them fatal—which have been reported have probably resulted from the use of too strong a solution. The author has used the following technique in 40 cases without any untoward results. A small preliminary intracutaneous injection of Abrodil is given in order to detect possible sensitivity to the drug; if the result is negative an injection of ephedrine is given. With the patient sitting, lumbar puncture is then performed and 2 cubic centimetres of 7 per cent Novocain (procaine hydrochloride) solution is introduced for the purpose of preventing the pain which is felt when Abrodil is injected without preliminary anaesthetization. The patient is then laid carefully on his side with the head and shoulders moderately raised by pillows. The lumbar puncture needle is left *in situ* and as soon as anaesthesia is complete, usually in about 10 minutes, 10 cubic centimetres of 20 per cent Abrodil solution is introduced. Plates are exposed with the patient in various positions, care being taken throughout that the head is kept high. Abrodil is rapidly absorbed, and the head must be kept raised only for a few hours after the examination. With this technique the only reaction has been transient headache which occurred in 2 of the 40 patients. Radiographic results were excellent.

The soft tissues

Technique of examination.—Radiology, according to Frantzell, can supply useful confirmatory evidence of oedema of the soft tissues. The varying degrees of penetrability by x-rays of soft tissues was early recognized and was utilized, for example, in demonstrating deeply seated lipomata. Special methods have been devised to improve visualization of the soft tissues, such as the use of soft rubber bags filled with water as filters. The author describes a series of observations which he has made in cases of thrombosis and other pathological conditions of the lower limb. It is necessary to use a much softer type of radiation than that used for radiology of the skeleton. The factors the author recommends are: focal distance, 150 centimetres; exposure time, 1.5 seconds; milliamperes, 300; kilovolts, 36–45. The normal appearances are as follows. The bones appear merely as shadows slightly more opaque than the surrounding muscles. The latter form a more or less homogeneous and featureless layer, but careful observation usually discloses strands of fatty tissue running between the individual muscles or muscle groups, and in old people much of the muscular tissue may have been replaced by fat. The normal superficial fascia is less dense than is the muscle layer, is finely reticulate in structure and is penetrated by vascular shadows. The fascia lata is seen as a fine line separating the muscular and fatty layers. A similar line about 1 millimetre in breadth, the cutis line, represents the skin. It is separated from the subcutaneous layer by a fine, darker line. In oedema the abnormalities seen are widening and coarse reticulation of the fatty layer and increased breadth and density of the cutis line. The change in structure of the superficial fascia and the widening of the cutis line can be better demonstrated after subcutaneous injection of physiological saline.

Skeletal system

Bony irregularities of the hands.—Holt and Hodges discuss the value of x-ray examination of the hands in the diagnosis of various diseases. The alterations of normal carpal, metacarpal and phalangeal structure reflect the presence of remote systemic disease, as well as purely local pathological processes, and are worthy of careful consideration. A single dorsal-

palmar projection of the hand usually gives more valuable information in this respect than do other parts of the skeleton because of the technical simplicity of the procedure, the absence of confusing overlapping shadows, and the relative rapidity of change in the bones of the wrist and hand during the maturation period. The hand changes are virtually diagnostic in certain cases—they are very characteristic in acromegaly, and an eosinophilic adenoma of the hypophysis may be suspected even without intrasellar erosion. Cretinism produces profound delay in epiphyseal ossification. Other endocrine dysfunctions cause characteristic lesions, and changes, said to be practically pathognomonic of primary prepuberal hypogonadism, have been described in the metacarpals and phalanges. Congenital abnormalities, such as those occurring in dwarfism and arachnodactyly, are shown by radiography. Slow spontaneous amputations of portions, or even the whole, of one or more phalanges occur in many trophic diseases, and the bones of the hands may be involved in various chronic granulomata. Long-standing chronic pulmonary or mediastinal disease produces pulmonary osteoarthropathy which in its severity, regression and progress varies directly with the degree of pulmonary involvement. Haemopoietic and blood diseases produce valuable x ray signs in the bones. Haemophilia causes articular irregularities in the larger joints, and the characteristic changes produced in the skeleton by erythroblastic anaemia are clearly demonstrated in the hand. Radiography of the hands in the diagnosis and prognosis of various types of chronic non-specific arthritis is of the greatest value, and osteopetrolisis, osteopetrosis and melorheostosis can be diagnosed by x ray examination of the hand alone.

Male genital tract

Vasoseminal vesiculography—Bertelsen and Wandall describe vasoseminal vesiculography and its clinical application. Considering the iodized oils to be unsuitable for use as contrast media owing to their persistence in the tissues and having demonstrated experimentally that Hippodol (a 50 per cent solution of sodium *ortho* iodohippurate) may damage the epithelium of the vas, the authors decided to use Perabrodil (diodone), which they had proved to be harmless, for vasoseminal vesiculography in 16 cases. In 6 of these the investigation was done during vasectomy and in the remainder for diagnostic purposes. The medium may be injected either into the vas by vasotomy or transurethrally into the ejaculatory duct. Obstruction of the vas was demonstrated in 3 patients whose inguinal hernias had been operated on by the Bassini method. Abnormal course of patent vas was shown in 2 patients having undescended testes, the vasa being remarkably tortuous from the inguinal canal to the ampulla. Incomplete development of the vesicles was noted in 1 patient with undescended testes, in 1 with aspermia after trauma to testis and epididymis and in 1 whose epididymis had been resected for epididymitis. The authors consider that vasoseminal vesiculography is indicated in the following conditions: (1) aspermia, in the investigation of which the result of subsequent operation is not compromised by damage to the seminal epithelium if Perabrodil is used, (2) seminal vesiculitis, in which risk of spread of tubercle bacilli by vesiculography is being investigated, (3) in a condition in which adults are about to undergo orchidopexy in order to ascertain whether the vas is or is not sufficiently long for the desired segment to be mobilized, (4) pain in the groin and testis after herniotomy, for the purpose of ascertaining whether or not it is due to a possible constriction of the vas.

General

In tropical disease—Garland describes some tropical diseases, those most likely to be found in temperate areas, in which radiology can be used with advantage in diagnosis or treatment. In malaria, the manifestations of which produce symptoms mimicking many and various diseases, help in diagnosis may be given in unsuspected cases by x ray examination. Enlargement of the spleen can be diagnosed when it is over 17 centimetres long or over 9 centimetres of the left kidney and elevation of the left side of the diaphragm. Because of severe pains in the joints x ray examination may be asked for in dengue, but there are no characteristic x ray findings. Changes in the colon, as well as abscesses in the liver and lung, may be seen in patients with chronic amoebic dysentery. In hookworm disease patients with ankylostomiasis may have duodenitis caused by the hooklets. The worms of ascariasis may be recognized as radiolucent shadows in the jejunum, and the gastro-intestinal tract of the worm itself may be outlined with the host's barium at a 12 hour or 24-hour study. In filariasis the tissues, lymphatic glands or scrotal lymphatic vessels. They have a different distribution from calcified *Trichinella* and are much smaller than *Cysticercus*. X ray treatment is of considerable benefit but does not cure. It gives excellent results in lymphuria. The larval form of the pork tapeworm causes cysticercosis and when calcified shows as small opacities in various parts of the body. In toxoplasmosis, a rare condition due to a sporozoön, the *Toxoplasma* various cerebral and pulmonary lesions of radiological interest have been reported. In Madura foot, a fungus infection, the bones and joints of the foot show destruction and osteoporosis.

Radiotherapy

X ray therapy

Effects of x rays on normal tissues—Hueper and de Carvajal Forero subjected dogs to a series of roentgen irradiations over the gastroduodenal region. The dogs were divided into two groups, one receiving a total of 4,875 within 25 weeks and the other, bigger doses up to

a total of 6,000 in 4 weeks. The prolonged irradiation in the first group produced an anaemia of secondary type and not a pernicious variety such as would have resulted if treatment had interfered with production of the intrinsic factor manufactured in the gastric mucosa. No significant lesions were noted in the mucosa and after cessation of the exposures the anaemia reverted rapidly to a transient erythrocytotic reaction. Apparently no permanent secretory damage was produced. The dogs in the second group showed marked loss in body weight, severe secondary anaemia and changes in the gastric mucosa causing loss of appetite, digestive disturbances and mucosal bleeding and perforating ulcers towards the end of the exposures. The chief cells of the gastric mucosa were found to be distinctly more sensitive to the action of the roentgen rays than were other cellular elements. The parietal cells were particularly resistant whereas the surface cells and glandular epithelium of the cardiac and pyloric regions were somewhat less so. Mucosal lesions included glandular mucoid cysts, atrophy and swelling of epithelial cells, interglandular oedema and fibrosis, submucosal oedema, congestion, fibrosis, hyalinization and leucocytic infiltration associated with vascular dilatation, arterial oedema and hyalinization. The arterial changes were considered to arise secondarily to the tissue changes caused in the gastric wall by the x-rays.

Grenz rays and diseases of the skin.—Bluefarb considers that grenz rays produce the greatest benefit in the treatment of superficial skin conditions. The rays are comparatively safe and may be used without fear of injuring important structures such as hair roots, sebaceous glands, sweat glands, testes and eyes. Grenz rays are recommended for the treatment of dermatoses of the scalp and the risk of producing epilation is almost non-existent. The whole body may be exposed at one treatment without giving rise to x-ray sickness or to blood diseases. Treatment may be repeated frequently and cumulative effects are negligible. There is not any danger to the operator and x-ray shock cannot occur. Temporary pigmentation sometimes develops and this is a serious drawback to treatment of the face and neck. A few cases of mild atrophy and telangiectasia have been reported but undesirable reactions and late skin injuries are rare provided that the dosage does not exceed 10 kilovolts and 10 milliamperes. Reactions are greatest in young patients, especially those with thin skins. Grenz rays are superior to x-rays in the treatment of naevus flammeus, blepharitis, lichen chronicus simplex and dermatitis of the external auditory canal, scrotum and penis. The rays are much more suitable for relapsing skin conditions such as mycosis fungoides, psoriasis, pruritus ani, atopic dermatitis, chronic dermatitis and seborrhoeic dermatitis of the scalp. Good results are obtained with fractional treatment. The initial dosage varies from 60 to 120 r but adults with naevus flammeus may be given from 1,000 to 2,000 r.

Vitamin treatment as a preventive of x-ray sickness.—Analogies having been observed between the syndrome of x-ray sickness, nausea, vomiting, headache, cramps and diarrhoea, and certain symptoms of pellagra and other dietary deficiency states, Bean, Spies and Vilter planned a comprehensive investigation into the effect of a standard dose of irradiation upon (1) normal well-fed subjects, (2) those given a vitamin B-deficient diet with and without supplements of some of the vitamins in which the diet was deficient and (3) upon pellagrins and other persons in whom a poor diet has caused general ill health. The authors describe some important results which already have been obtained, although the investigation is being continued. The radiation was given in all cases after an over-night fast of 13–16 hours. Four hundred x-ray units were administered to an area over the spleen and upper abdomen from a distance of 20 centimetres. It was found that in persons on a diet poor in vitamin B complex x-ray sickness developed which could be prevented, wholly or in part, by giving nicotinic acid or thiamine (aneurine) for a few days before irradiation; the same x-ray dose had little or no effect on well-fed persons. In a case of carcinoma and myomata of the uterus the patient was given repeated x-ray treatment which was invariably followed by severe irradiation sickness. She was not given nicotinic acid or thiamine and fulminant pellagra developed within a year. From the few cases already studied Bean, Spies and Vilter conclude that the best time for vitamin treatment is before, and not after, irradiation sickness appears, and that such treatment is essentially preventive.

X-ray and radium therapy

Used in nasopharyngeal conditions.—Ashbury reports on radiation therapy given to 157 patients for removal of nasopharyngeal lymphoid tissue. About one-third of the number were under 15 years of age. The average patient was found to tolerate 800–1,200 tissue roentgens, administered slowly and cautiously to the nasopharynx and pharynx within 4–5 months. This dosage was sufficient for young children. For older patients, the author devised an applicator for introduction through each nostril into the nasopharynx of 25 milligrams of adequately filtered radium to deliver a dose of 75 milligram hours. This supplementary γ radiation allowed a reduced roentgen tissue dosage and there were superior end-results. The basic procedure evolved was to administer x-ray treatments on the first, fourth, eighth, twenty-second and twenty-ninth days and a radium application on the fifteenth day. The physical factors employed were: 200 kilovolt peak, 60 centimetres target skin distance, 0.5 millimetre copper filter, 10 centimetres diameter round cone, and 125 r to each of two ports, one on each side of the face and neck. Gratifying results were obtained in the treatment of conduction deafness in children when lymphoid tissue had obstructed the pharyngotympanic orifices, and in the treatment of respiratory obstruction and infection. Lymphoid tissue

fractures and sclerosis of the pelvis. Commenting upon these cases the writers state that it has been shown that irradiation may affect all bones of the pelvis as well as the femur.

Skin circulation.—Pendergrass, Hodes and Griffith describe the changes in the minute vessels of the skin after exposure to x-rays. The areas studied were marked on the forearm by inking a circular die and pressing it gently on the skin. Each circle was covered with cedar oil and observed through a microscope with an Ultrapak attachment. The forearm was placed at the level of the lower portion of the sternum in order to avoid the hypostatic movement of venous pressure. The capillaries in the marked area were counted, and the visibility of the subpapillary venous plexus was noted. This procedure was repeated 6 hours after exposure to x-rays and on the next day. Subsequently, a drop of histamine, 1 in 1,000, was pricked into the skin near the area, so that the flare included the region studied previously. A final count was made and the number of capillaries visible at each of the previous examinations was expressed as a percentage of this amount. Controls were used for comparison. It was found that the differences in the responses were related to the method of irradiation. Thus, in one group, with a total of 333 roentgens delivered in $\frac{3}{4}$ minute at 200 kilovolts and a target skin distance of 15 centimetres, the dilatation of the capillaries observed after 6 hours had largely gone after 24 hours. In another group 308 roentgens were delivered in 30.8 minutes at 200 kilovolts and a target skin distance of 50 centimetres. With this radiation there was no significant dilatation of the capillaries but the effect on the subpapillary venous plexus was maximal. It is suggested that the variations were due to the degree of injury or to a neurotropic effect on the arteriovenous anastomoses.

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RECTUM DISEASES

See also B.E.M.P., Vol. X, p. 502; and Cumulative Supplement, Key Nos. 1346-1356.

Prolapse

Treatment

Rectal prolapse in women.—Chapple describes an abdominal operation for prolapsed rectum in a female patient. The operation was performed through a lower median incision with the subject in the Trendelenburg position. The pelvic bowel and rectum were drawn up and, using a Lane's cleft-palate needle holder, the recto-uterine pouch was obliterated and the bowel was suspended to the floor and the posterior aspect of the vaginal wall with No. 2 silk stitches, inserted in several tiers. Care was taken to avoid perforation of the bowel wall and the anterior aspect of the bowel was ultimately supported upon the upper part of the posterior wall of the vagina and upon the lower third of the neck; precautions were taken against the creation of any peritoneal pocket into which the small intestine might prolapse. In order to avoid possible obstruction by looping, the pelvic bowel was further spread out and was attached to the posterior aspect of the left broad ligament and out to the pelvic wall, avoiding the uterine tube and ureter. In Chapple's case the uterus was firmly suspended by plecting the round ligaments, drawing the silk sutures out through the sheath of the rectus and sewing them to it. The author adds that if, in order to obtain adequate support, he had considered it necessary to attach the bowel to the posterior surface of the uterine body, he would have ligatured the uterine tubes and fixed the uterus into the abdominal incision with silk sutures. For 7 days a residue-free diet should be administered and the bowel should be left alone; after that liquid paraffin and a small glycerin enema may be administered. In the event of any future pregnancy Chapple holds that it would be advisable to perform a Caesarean section so as to prevent any possibility of a recurrence of the prolapse.

Injuries

Penetrating wounds

Impalement of the rectum.—Impalement of the rectum is found most often among adult farm

workers Hutchins describes one case in a young girl living in a city who was impaled upon a hook of a lawn mower grass-catcher. Miners, ditch diggers, masons, carpenters and window-cleaners are also liable to this misfortune. Anatomical configuration of the buttocks contributes to the facility by which blunt objects may forcibly penetrate into the rectum. As a rule, the anterior rectal wall is injured. Every case is potentially fatal. When the perforation is peritoneal the mortality is 78.5 per cent, when extraperitoneal, major complications may still ensue although mortality is much less. The initial symptoms of pain and distress are remarkably slight and the gravity of the case may not be recognized until signs of peritonism appear. A careful digital examination should be made in order to ascertain the size and depth of any perforation present. If none is found a proctoscopic examination should be made, and then an x-ray examination in the left lateral position for detection of air in the abdominal cavity. Urine and faeces must be carefully examined. If a perforation of the peritoneum is found, a laparotomy must be performed at once in order to discover and repair the damaged tissues.

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RELAPSING FEVERS

See also B E M P., Vol. X, p. 584, and Cumulative Supplement, Key Nos. 1361 and 1362

Tick relapsing fever or non-epidemic relapsing fever

Clinical picture

Neurological complications—Scott states that neurological complications occurred in 9 of 41 cases of relapsing fever which were observed during the campaigns in the Libyan desert. The type of relapsing fever was not previously known in Egypt. Infection was transmitted by the bite of an unnamed argasid tick resembling *Ornithodoros erraticus*, the vector of the Tunisian strain of *Borrelia recurrentis*. This tick probably inhabited the burrows of desert rodents and infection was commonly acquired in caves, slit trenches and tombs. Investigations have shown that *Bor recurrentis* has neurotropic characters which produce meningo-vascular lesions in the pia arachnoid and the brain substance. Histological examination reveals haemorrhages and perivascular infiltration with mononuclear cells. Neurological complications occurred at any time during the course of the illness but especially after the third week. Repeated relapses ensued in some cases but the majority of patients recovered completely, and there were no deaths. Treatment with arsphenamine was ineffective in reducing the number of relapses or the liability to invasion of the nervous system. The manifestations of meningitis predominated in one group of patients and signs of focal nervous damage were noted in another group. Some patients had the signs and symptoms of both groups. The various forms of paresis included a right hemiplegia, a right abducens palsy and 2 cases of facial paralysis. In some cases the features were rather those of intracranial hypertension than of meningeal irritation. A lymphocytic pleocytosis was the characteristic finding in the cerebrospinal fluid. The total cell count was sometimes as large as 2,000 per cubic millimetre and there was a rise in the total protein and globulin. In one instance *Bor recurrentis* was seen in a dark ground preparation. The Wassermann reaction of the cerebrospinal fluid was tested in 3 cases and found to be negative. Kahn tests of the blood were negative in all cases.

Scott, R. B. (1944) *Lancet*, 2, 436

RESUSCITATION

See also B E M P., Vol. X, p. 596

Methods of resuscitation

General

A new method—Viswanathan describes a new method of artificial respiration. The operator, standing behind the patient's head, places his palms on the lower thoracic wall. The middle fingers being on the anterior axillary lines then with fingers hooked round the lower costal margins exerts steady traction upwards and outwards for 3 seconds, thereby raising the anterior portions of the ribs and widening the costal arches. Traction is then released and the chest is gently pressed downwards and inwards, while the extended fingers exert the same pressure on the abdomen. Intermittent traction 12–15 times a minute brings about a respiratory exchange of over 7,000 cubic centimetres of air. Comparative amounts of air expired Schaefer's, Silvester's and Viswanathan's methods of artificial respiration were respectively 278, 425 and 836 cubic centimetres. The considerable difference in pulmonary ventilation is attributable to the new method assisting both the inspiratory and expiratory processes. The author reports on a case emphasizing that this method also helps to restore the circulation, because the venous return is aided. The method is easy and puts less strain on the operator than do other methods.

Viswanathan, R. (1945) *Lancet*, 1, 238

RETINA DISEASES

See also B E M P., Vol. X, p. 611, and Cumulative Supplement, Key Nos. 1364–1379

Vascular diseases

Venous thrombosis

Effect of dicoumarol—Crawford and Nassim describe unusual occurrences in dicoumarol

(3 : 3'-methylene-bis (4-hydroxycoumarin), dicoumarin) treatment of right retinal thrombosis in a 19-year-old and apparently otherwise healthy soldier. Three hundred milligrams of dicoumarol were given followed by 200 milligrams daily for 12 days when prothrombin time had increased to only 30 seconds; therefore 250 milligrams were administered on the fourteenth day and 300 milligrams on each of 3 succeeding days. Prothrombin time was now 36 seconds. Since loin and abdominal tenderness had developed and blood urine showed a heavy protein cloud, and ordinary specimens hyaline and granular casts and erythrocytes, administration of dicoumarol was stopped. Two days later prothrombin time rose to 39 seconds and gross haematuria and subconjunctival haemorrhage in the right eye occurred. Transfusion of one pint of fresh blood reduced the prothrombin time to 29 seconds, but haematuria persisted. On the fourth day after administration of dicoumarol had been stopped the prothrombin level reached 47 seconds, haematuria increased and subconjunctival haemorrhage extended in the right and appeared in the left eye. Further transfusions reduced prothrombin time to 22 seconds and urinary signs gradually disappeared. Dicoumarol had no apparent effect on the retinal lesion and its action persisted long after its administration ceased. Symptoms of intolerance were much delayed.

Diabetic retinitis

Ophthalmoscopic appearances

Association of diabetic and hypertensive retinitis.—The retinal changes associated with diabetes and hypertension are discussed by Ballantyne who does not believe that these retinopathies are identical. Ophthalmologically the earliest changes in both conditions are found in the finer retinal vessels; in diabetes the changes tend to affect the venous side and in hypertension the arterial side is affected. The author found in one-third of a series of diabetics that the retinal veins were enlarged and tortuous. The occurrence of globular aneurysms on the retinal capillaries around the macular area is believed by Ballantyne to be the earliest unequivocal sign of diabetes. In diabetes swelling of the endothelial cells in the capillaries, sometimes causing almost complete blockage, can be microscopically observed and the larger veins show swellings and fatty deposits at their junctions or bifurcations and a tendency to form saccular aneurysms. In hypertension fatty deposits are also found but they tend to form in the media and adventitia. Diabetes, moreover, causes beading expansions and loops in the large veins; the main microscopical lesion is a phlebosclerosis. Diabetic exudates are found primarily in the centre of the fundus and usually in the deep layers. In hypertension they are generally circumpapillary in position. Ballantyne suggests the possibility that there are stages in the development of diabetic retinitis, beginning with fatty infiltration and swelling of the endothelium of the smaller vessels with, later, capillary and venous stasis, the formation of capillary aneurysms, phlebosclerosis, thrombosis in capillaries and small veins, haemorrhage and exudates. He points out that the two conditions may coexist—half the number of diabetic patients in this series had hypertension—and that the retinal picture will often reflect the composite nature of the general disease. It is possible that toxic factors may be responsible for the initial vascular changes in both conditions.

Macular lesions

Degenerative

An unusual type of foveo-macular retinitis.—Cordes relates foveo-macular retinitis with Duke Elder's central serous retinopathy and Gifford's central angiospastic retinopathy. His report is based on approximately 176 naval men who served in the Pacific combat area, but the condition has been described in civilians and in patients at enlistment centres. The author describes the fully developed form as "a hole or cyst in the fovea surrounded by a gray area, 0.5 to 1 disk diameter in size, the gray area being due to fine granular pigment". Small multicystic areas of degeneration may appear, which give the fovea a honeycombed appearance. A typical hole in the macula may develop. There are scotoma covering the area of the pigimentary change and varying visual disturbance. Symptoms are: pain in the back of the eye and boring headache on the affected side which may persist for 4 months and may be increased by heat or bright light; photophobia; sensation of presence of foreign bodies. Asymptomatic and therefore unrecognized cases probably occur. Aetiology is debated but most observers agree that angiospasm, probably in vasomotor unstable subjects—especially those who smoke to excess—warrants most consideration and investigation, specially in relation to peripheral vascular disease. The pathology of foveo-macular retinitis is thought to be a fluid exudate which occurs after a probably angiospastic vascular change and is usually absorbed quickly. If the oedema persists for long, pressure on conducting fibres leads to secondary degeneration and lowered visual acuity. Drusen formation may occur. Of various treatments the only ones which seemed to be beneficial were, in early cases, administration of sodium nitrite and vitamin A (200,000 units daily), and in other cases the giving of nicotinic acid (25 milligrams intravenously, twice daily) and the immersion of the feet in a hot (110°) bath for half an hour in order to maintain the dilatation. Administration of sedatives and the discontinuance of smoking by the patient are recommended. Prognosis is generally good. Many patients retain 20/20 vision despite gross macular changes. Some observers, however, are less optimistic about permanent improvement.

Detachment

Clinical picture

End results of 120 operations.—Describing the end results of 120 operations at a base hos-

pital for retinal detachment, Hine reports on 50 successes. A large proportion of bad risks came from one source, and from other sources the author had 71 patients with 35 successes—a percentage of 49.29, which may be taken as the correct figure for unselected hospital cases if the patients are operated on in satisfactory surroundings. Hine defines a successful result as full reattachment of the retina with full peripheral field. All successful cases were observed for at least a year. Of all cases 10.8 per cent had had previous detachments in the other eye, which was blind, and the author believes that the frequency of bilateral detachment is an added reason for advising operation when the other eye is a good one. Myopia was present in 48 per cent of cases. There was a history of trauma in 13.88 per cent. When the series was divided into two groups, one over and one under 40 years of age, there was no practical difference in the number of successes. Hine believes that in no selected series of cases should the chance of success be put higher than 75 per cent, and also—in view of unexpectedly successful results in some apparently unpromising patients—that there are few patients who should not be given the opportunity of operation if they are willing to take the attendant risk.

Ballantyne, A. J. (1945) *Arch. Ophthalmol.*, N.Y., 33, 97

Cordes, F. C. (1944) *Amer. J. Ophthalmol.*, 27, 803

Crawford, T., and Nassim, J. R. (1944) *Lancet*, 2, 404

Hine, M. L. (1944) *Brit. J. Ophthalmol.*, 28, 575

RHEUMATIC INFECTION, ACUTE

See also B.E.M.P., Vol. X, p. 639, and Cumulative Supplement, Key No. 1380

Aetiology

Relation of rheumatoid arthritis to acute rheumatism

Young and Schwedel in a detailed study of 38 necropsy cases review the evidence regarding the aetiology of rheumatoid arthritis and of rheumatic heart disease, the causation of both being at present unknown. A common aetiological background has been accepted in Europe but not in the United States of America where the diseases have been held to be two distinct clinical conditions present together in the same patient. In the authors' series of 38 cases in adults 33 patients were found to have cardiac lesions which were not the result of hypertension or of coronary artery disease. Of these 33, 24 had rheumatic valvular disease, 10 of them having pericarditis as well. The diagnosis of rheumatic heart disease was not made in 14 of 32 cases and the diagnosis of rheumatic valvular disease was not made in 6 cases although in the course of their long illness these patients had been examined frequently by many observers. The clinical history of these 33 cases was closely studied. Only 3 gave a history of frank rheumatic fever earlier in life. In one patient at the age of 32 joint deformity developed. By repeated attacks of polyarthritis, she had evident deformity of the joints at the age of 39 when she was admitted to hospital because of acute rheumatic fever, from which she died. In 18 cases it was possible to determine the time interval between the onset of the joint deformity and the discovery of heart disease. In 14 cases joint deformity preceded by an average of 8 years the discovery of heart disease, in 2 cases heart disease was discovered first and in 2 other cases cardiac and joint disease were discovered concomitantly. In 1881 Charcot concluded that "these are not two fundamentally distinct diseases, but two manifestations of one and the same diathetic state". Adding their own data to those of other observers, the authors conclude that an extremely close relation exists between rheumatoid arthritis and rheumatic fever. On account of the restricted life imposed on these patients because of their joint deformities, the severity of the cardiac lesions had only a minor place in the clinical picture.

Clinical picture

Rheumatic peritonitis

A clinical study—Digestive, pseudo-appendical or peritoneal symptoms may precede, coincide with, or follow other manifestations of rheumatic fever, and have been noted by numerous observers. Berger in a clinical study on 4 cases of the disease presents the abdominal signs and symptoms which occurred, all subsided with administration of salicylates. Abdominal disease preceded either manifest clinically recognizable acute rheumatic fever, rheumatic heart disease, or subacute bacterial endocarditis. No patient had any history of peritonitis, previous rheumatic fever or heart disease. In one case subjected to laparotomy the entire peritoneum was oedematous and injected. The appendicular peritoneal surface was involved but not more severely than was the adjacent ileum or parietal peritoneum. On microscopic examination the mucous membrane of the appendix was found to be intact and there were many lymphocytes and polymorphonuclear leucocytes in the subperitoneal area. Culture from the abdomen was sterile. The day after the patient had been discharged from hospital the original symptoms of abdominal pain and fever reappeared, a few days later tender nodules on the legs and elbow were observed and later multiple arthritis developed. In cases of abdominal disease in which the diagnosis is of diffuse peritonitis the treatment of choice is usually conservative and that a therapeutic test of large doses of salicylates can safely be made providing there is neither septic temperature, nor localized mass, nor tenderness or rebound tenderness constantly referred to one area such as McBurney's point.

Diagnosis

Main diagnostic manifestations

Until the aetiology of rheumatic fever is known or there is a specific diagnostic test, some confusion in diagnosis is inevitable. Jones suggests that a verified history of rheumatic fever plus any combination of the major manifestations of the disease, namely carditis, arthralgia, chorea and nodules, constitute reasonably certain diagnostic criteria. Alternatively, the diagnosis is not usually in doubt when at least one of the major manifestations exists with two of the minor. These he lists as fever, abdominal or praecordial pain, erythema marginatum, epistaxis, pulmonary changes and laboratory abnormalities such as microcytic anaemia, leucocytosis and increase in the sedimentation rate, all of which are non-specific. Jones considers that response to salicylates or a history of great familial incidence of the disease cannot be considered to be more than a suggestive contribution to diagnosis. The presence of rheumatic heart disease increases the diagnostic significance of the minor manifestations. Only three clinical syndromes—Still's disease, disseminated lupus erythematosus and the acute form of rheumatoid arthritis—cause confusion in diagnosis when a combination of major signs is present. Rheumatic fever and rheumatoid arthritis may coexist in a small number of cases. Geographical incidence and age cause variations in the problems of differential diagnosis. Jones cites the observation of Hansen that, in children, abdominal pain simulating appendicitis offers the most common difficulty, then poliomyelitis, osteomyelitis, varied dermatoses and nephritis. Other confusing diseases are tuberculosis, undulant fever, meningococcal septicaemia, gonococcal arthritis and gout. Rheumatic fever constitutes a serious medical problem among the United States armed forces.

Treatment

Preventive

Review of three main methods.—Thomas reviews various methods of preventing the recurrences of rheumatic fever. Tonsillectomy is largely ineffective since infections of the pharynx with β haemolytic streptococci continue after operation. The sending of patients to geographical zones which are free from haemolytic streptococci, although effective, is limited as a popular method of prevention. After the experiments of Buttle and his collaborators in 1936 which showed the value of small doses of sulphanilamide in preventing β haemolytic streptococcus infections in mice, several workers applied the knowledge to rheumatic fever patients. Thomas states that prophylactic sulphanilamide, in daily doses of about 1 gramme, has been given over the course of 7 years for a total of 815 patient seasons—usually October to June. Only 1 per cent of recurrences was noted against 10–35 per cent in control groups. From December 1943 to March 1944, about 250,000 men were given prophylactic sulphadiazine, in doses of about 1 gramme daily, by the United States naval authorities. An equal number of men acted as controls. The attack rate of rheumatic fever under prophylactic treatment decreased gradually, showing a lag as compared with the attack rate of scarlet fever, which corresponds with the conception of a latent period between the original bacterial invasion and the allergic manifestations when rheumatic fever appears. The attack rate was 14 times less than in controls. The author reviews briefly two other methods of prevention, namely by injections of a filtrate of haemolytic streptococcus and by prophylactic doses of salicylates, but considers that sulphonamides offer the greatest hope; sulphadiazine is probably the compound of choice. The compound should be started in convalescence and continued daily for at least 5 years. Toxic reactions have been remarkably rare in the experiences quoted. When agranulocytosis occurs it is usually in the third or fourth week, so that leucocyte counts are necessary at this stage.

Remedial

Ineffective use of penicillin.—Watson, Rothbard and Swift gave penicillin in doses varying from 1,975,000 to 3,470,000 Oxford units to 8 young adults with acute rheumatic fever without apparent alteration of the course of the disease. All the patients were acutely ill with elevated temperatures and polyarthritis and 2 had pericarditis. On admission to hospital, group A haemolytic streptococci were isolated on culture from the nasopharynx of 6 of the 8 patients. The addition of 0.015 Oxford unit of penicillin completely inhibited growth of these organisms when it was added to cultures containing 1,000–5,000 bacterial cells. Many times this concentration of penicillin was maintained in the patients' blood during treatment and the group A haemolytic streptococci were eliminated permanently from the nasopharyngeal mucous membrane of the patients. The authors therefore consider that the dose of penicillin was adequate and that the drug can be considered to be ineffective in the treatment of rheumatic fever. As they point out, experiences do not preclude the possibility of penicillin influencing the early stages of the disease, namely the initiating streptococcal infection and the quiescent period. It would seem that, in susceptible persons, once the preliminary streptococcal infection has started the mechanism leading to the onset of rheumatic process the antibacterial agents now available do not materially alter the evolution of that mechanism. This presumably is because either there are bacteria or viruses other than group A streptococci involved in the production of the disease which are resistant to penicillin (and to the sulphonamide drugs), or deep-seated foci of streptococci may exist which require considerably larger doses of penicillin for their eradication than do those which remove the organisms from accessible mucous membranes. No definite toxic manifestations to penicillin were observed in any of the 8 patients who were treated.

and in another group taking daily doses of the cod liver oil issued by the Ministry of Food. The calciferol method is not only economical, but also reduces work and saves time. In the case of infants under the age of one year it may be advisable to repeat the dose after 3 months if the first one was given in the autumn or winter. Premature infants and those taking thyroid gland or growing rapidly after an acute illness may require a double dose. Massive doses are not recommended in cases of renal disease owing to the risk of producing metastatic calcification.

Krestin, D. (1945) *Brit. med. J.*, 1, 78.

SCARLET FEVER

See also B.E.M.P., Vol. XI, p. 1; and Cumulative Supplement, Key No. 1387.

Bacteriology and morbid anatomy

Dissemination

Airborne infection.—Hodes, Schwentker, Chenoweth and Peck discuss scarlet fever as an airborne infection. Scarlet fever is caused by a strain of group A β -haemolytic streptococci, practically all strains of which can cause local infections of the throat and adjacent structures of the respiratory tract. The members of the group are divisible into more than 40 serologically distinct types. Some strains elaborate toxins which produce the rash and other systemic disturbances of scarlet fever; with other strains streptococcic tonsillitis develops. Some strains spread readily in a population group, the amount of illness caused by each strain being dependent on its disseminating ability. Dissemination is influenced by climate, being slight in summer and autumn and great in winter and spring, and is markedly reduced by the use of sulphadiazine in prophylactic doses of 1 gramme daily. Although the reason is not clear, sulphadiazine appears to prevent implantation of the streptococci in the respiratory passages. Outbreaks of streptococcal throat infections due to contaminated milk and other foods have been noted, but infection is usually airborne and is most likely to be conveyed to individuals who come into close proximity with a carrier or a patient and who by so doing inhale streptococci from the upper respiratory passages of such persons. For example, streptococci have been recovered from cough plates held to within 2 feet of the mouth of a scarlet fever patient, but beyond this distance no streptococci were recovered. Less directly infection may be conveyed by inhalation of streptococci floating in the general air reservoir of a room.

Treatment

Specific

Sulphonamides, commercial antitoxin and convalescent serum.—In an article on the treatment of scarlet fever, Fox and Gordon compare the results obtained by the use of sulphonamides, of commercial antitoxin and of convalescent serum. The cases studied were taken from those which were treated at the South View Hospital of the City of Milwaukee Health Department during the 6 years from 1937 to 1943. Out of a total of 7,500 cases 1,000 patients had received pooled human convalescent serum. As controls, 1,000 consecutive cases were selected from those which occurred in 1923, a year in which antitoxin, convalescent serum and sulphonamides were not available. It was found that sulphonamides, although they were of value in the treatment of certain complications, were of no use in the toxic phase of scarlet fever, and that commercial antitoxin, which was prepared with horse serum, although it was useful in the toxic phase, might cause foreign protein reactions. Pooled human convalescent serum gave the best results, causing rapid drop of temperature—the average duration of pyrexia even in severe cases was only $2\frac{1}{6}$ days—alleviation of signs and symptoms, avoidance or improvement of complications, a shortened stay in hospital and a lower mortality rate. In certain complications the use of sulphonamides together with serum, is of advantage. Six years' experience of the use of convalescent serum showed that smaller doses were as effective as were the larger doses formerly used, especially if the serum were given early in the illness.

Fox, M. J., and Gordon, N. F. (1944) *Arch intern. Med.*, 74, 1.

Hodes, H. L., Schwentker, F. F., Chenoweth, B. M., Jun., and Peck, J. L., Jun.
(1945) *Amer. J. med. Sci.*, 209, 64.

that pericarditis was a manifestation of the disease. Other changes included the typical skin lesions of scleroderma and a widespread arteritis. Diffuse glomerular and arterial lesions were found in the kidneys. It is concluded that scleroderma is a disease which is characterized not only by connective tissue overgrowth but also by muscle atrophy and degeneration with or without connective tissue replacement. The changes in the muscles are related to some of the clinical manifestations but bear no direct relation to the lesions of the vascular system.

Bevans Margaret (1945) *Amer J Path* 21 25

SCURVY

See also B E M P Vol XI p 44

Morbid anatomy

Ascorbic acid deficiency and the kidneys

Effect on alkaline phosphatase—The effects of ascorbic acid deficiency on the activity of alkaline phosphatase in guineapig kidneys has been investigated by Russell Rouse and Read. This experiment follows a previous observation by the same authors who found that the proximal convoluted tubules of the kidneys contained less alkaline phosphatase in tuberculous scorbutic guineapigs than they did in the control group. This experiment was designed on approximately the same lines but the tuberculosis factor was left out. Blocks of kidney tissue and the mucosa of the small intestine were studied comparatively from three groups of guineapigs. These were (1) a control group on a diet lacking vitamin C with a maintenance daily dose of 0.3 milligram of ascorbic acid (2) an inanition group which was given the same daily dose of vitamin C but food was withheld so that they lost weight comparatively to the scorbutic group and (3) a group which was fed on a diet lacking vitamin C. All the animals were killed 19 days after the start of the experiment. The tissues were studied by the histochemical methods of Gomori and Takamatsu. The authors found there to be a definite diminution in the alkaline phosphatase in the proximal convoluted tubules of the kidneys of the scorbutic group as compared with the control groups of animals. This paralleled the result of the previous experiment. Little difference was found in the activity of alkaline phosphatase in the mucosa of the small intestine in the three experimental groups. The authors conclude that such a decrease of the activity in the alkaline phosphatase cannot be correlated with any known physiological function of the kidney but that these results confirm the findings of other investigators who use chemical methods.

Clinical picture

In adults

Periosteal lesion—Evans, discussing the periosteal lesions in scurvy, states that in the time which has passed since the disease was described it has become clear that subperiosteal lesions are a late manifestation and the earliest changes appear in the metaphysis. In the years 1936–1941 93 cases of scurvy were diagnosed at the Children's Hospital of Detroit, Michigan, and he remarks that the disease is not rare, that no cases occurred before 7 months of age and that 90 per cent of the patients were aged between 7 and 13 months. The earliest radiological changes described—ground glass type of demineralization and the signet ring appearance of the epiphysis—were seen very often but the author holds that these signs are not sufficiently specific to be regarded as being pathognomonic of scurvy. The submetaphyseal notch, stated to be pathognomonic of the disease, was seen in 89 per cent of the cases. Fragmentation or separation of the metaphysis was seen in 42 per cent of cases. Two types of periosteal shadow were seen: (1) a narrow triangular shadow with its base at the metaphysis and extending some distance along the shaft was observed in 39 per cent of all cases, and (2) a much larger and usually club-shaped shadow associated with the displacement of a large portion of the metaphysis and epiphysis was seen in 17 per cent of cases. Evans discusses the differential degrees of the two diseases when they coexist. Rachitic changes are usually most pronounced in the distal ulnar metaphysis whereas scorbutic lesions occur more often on the radial side. The differential diagnosis from syphilis, tuberculosis and pyogenic osteomyelitis usually presents no radiological problems. Epiphyseal displacements with subperiosteal haemorrhages, usually the results of birth injury, may sometimes be seen to be not unlike the epiphyseal displacement of advanced scurvy. The author concludes that pathognomonic radiological signs depend for their occurrence, location and severity upon the severity of the lesions which are present in the metaphyseal areas of the long bones.

Treatment

Effect of ascorbic acid

McMillan and Inglis report investigations of 53 patients with scurvy. There were 48 males and 5 females and all but 2 lived alone. The ages ranged from 41 to 82 years. The most important aetiological factor, notably in males, was ignorance of the need of vegetables and potatoes in the diet. There was also a tendency to omit these foods because they required preparation and cooking. Poverty accounted for inadequate diets, poor lodgings and lack of facilities for cooking. In some cases wartime scarcity of fruit precipitated the onset of the disease. In 80 per cent of the patients the time which elapsed between the first sign or symptom and admission to hospital was less than one month. All patients had skin petechiae and

23 had deeper haemorrhages in both legs. Signs appeared first in one leg, then in the other and finally in the arms. The only unusual complaint was lumbago, and this was possibly due to small deep haemorrhages in the muscles of the back. Positive pressure cuff tests were not diagnostic and the results were unrelated to the plasma ascorbic acid level. The vitamin C content of the urine was deficient and the amount of plasma ascorbic acid was compatible with clinical scurvy. The blood picture showed an anaemia varied in type but mainly normocytic in character. The anaemia was considered to be nutritional in origin but not to be due to lack of vitamin C alone. Bone marrow changes were not specific. Administration of ascorbic acid quickly improved the scorbutic manifestations. It is suggested that, as a prophylactic measure, the concessions allowed by the Ministry of Food to children and expectant mothers should be extended to the elderly. Moreover, the aged poor need clean cheap lodgings with canteen facilities and local authorities should give practical consideration to the provision of such amenities.

Evans, W. A., Jun. (1945) *Amer. J. Roentgenol.*, **53**, 147.

McMillan, R. B., and Inglis, J. C. (1944) *Brit. med. J.*, **2**, 233.

Russell, W. O., Rouse, E. T., and Read, J. A. (1944) *Arch. Path.*, **38**, 40.

SENESCENCE AND SENILITY

See also B.E.M.P., Vol. XI, p. 69; and Cumulative Supplement, Key No. 1394.

Normal old age

The circulatory system

The heart of old age.—Freedberg and Lewis, emphasizing the occasional difficulty experienced in differentiating between disease and normal senescence, discuss the normal hearts of old age. They deny any correlation between coronary artery disease and changes in the radial arteries, and warn against describing as angina pectoris a chest pain which may be due to cervical or thoracic osteo-arthritis, hiatus hernia or gallbladder disease. The importance of careful history taking is stressed. The systolic hypertension of old age is probably compensatory and Russek's statement that the life expectancy of persons with systolic hypertension is the same as that of persons with normal blood pressure, is quoted. It should be remembered that age alone may be associated with rise of corrected erythrocyte sedimentation rate. There is disagreement amongst investigators concerning what is a normal electrocardiogram in healthy old age; radiological evidence of significant or progressive increase in heart size may indicate cardiac disease, even in the aged. The authors consider that all elderly persons should be regarded and treated as victims of some degree of coronary arteriosclerosis even in the absence of clinical evidence. Prevention of postoperative acute myocardial infarction depends upon avoidance of shock resulting from haemorrhage and severe infection, and the fact that the primary cause of death in aged surgical patients is seldom the heart, is specially noted. Freedberg and Lewis stress the deleterious effects upon normal hearts, especially in old people, of anaemia and nutritional deficiencies, correction of which may help to ward off such complications as angina pectoris and congestive heart failure. Although they do not agree with Dock that rest in bed "claims more lives than all other therapeutic agents added together", the authors urge the great importance of good clinical judgment in avoiding cardiac weakness and atrophy as well as pulmonary and other complications, due to prolonged and absolute rest in bed. A warning is given of the danger to the aged of severe physical or emotional strain.

Senile deafness

Aetiology.—Fowler discusses the causes leading to the ageing of the ear. The difficulty is to determine which processes are physiological, causing normal ageing, and which are pathological, causing premature ageing. The fundamental cause of ageing is not simple; it involves action and reaction of the various factors such as heredity, detrimental influences, environment, vascular disease and alterations in hormonal, metabolic and nervous functions. The body as a whole ages in response to loss of function but is left with just sufficient for senile needs. The auditory mechanism is well adapted for detecting slight and progressive loss of function. The otic capsule is early developed to adult dimensions before birth, soon afterwards attaining its highest efficiency and thereafter declining slowly. The human external ear is of little functional importance. Thinning of the drum membrane increases with age but unless associated with loss of tension, hearing is not impaired. Atrophy or involutionary processes may alter the structure of the muscles, tendons and ossicles of the middle ear with consequent loss of function. Tests now in use are too crude to measure the gradual changes that occur in the function of the vestibular apparatus of the ear although the acuity of hearing can be measured by audiometric tests. The progressive loss in the capacity for hearing varies with age and with frequency (for air conduction). The frequency region near 4,000 cycles per second air conduction appears to be affected more than do the frequency regions above and below it. It is possible to ascertain the average deviation from the normal for any age or decade. The loss of vibratory sense may account in part for a loss of bone conduction. Increasing deafness in ageing people may be due not so much to otosclerosis as to neural lesions, the sclerotic condition remaining almost stationary while the nerve deafness increases.

Pathological old age

Clinical picture

Normal and abnormal old age.—East distinguishes between senescence, which is normal old

age, and senility in which the impairment natural to age is excessive, with pathological mental and physical changes. Although it is sometimes difficult to differentiate between the two at first there are obvious differences when the senile process becomes more advanced. The chronological age of an individual is no indicator of the onset of senescence. In what might be called physiological old age there is a gradual lessening of the intellectual, emotional and volitional attributes of the mind. In senility the impairment is much greater, initiative and judgment fail, and there is confusion of thought, depression, disordered sleep, anxiety, unwarranted suspicions and distrust, restlessness and restiveness. The development of senility seems to depend upon the inherent constitutional make-up of the individual, upon the presence of cerebral arteriosclerosis and upon stresses experienced during life, as well as upon lifelong nervous symptoms and, indirectly, upon the manner of life. In Great Britain and in the United States of America reports show that in the 10 year period 1929-1938 there has been a marked diminution in crime among persons of the age of 60 and over. The greater security given by old age pensions in Great Britain and the generally improved social conditions in both countries have contributed to the smaller incidence of crime. As the individual ages personality is a more important criminogenic factor than is environment, stereotyped behaviour patterns having an important influence on many lives. Of late, more interest has been taken in the problems of old age, and still more study and investigation is needed to give the ageing the best chance of a useful and happy decline. Interests and work suitable for diminishing strength and resilience, suitable recreation and opportunity for social service should be available for all. Loneliness and egotism produce much unhappiness in old age. Understanding of the problems of the ageing will help greatly in dealing justly and sympathetically with the aged criminal.

East, W. N. (1944) *J. ment. Sci.*, **90**, 835.

Fowler, E. P. (1944) *Arch. Otolaryng.*, Chicago, **40**, 475.

Freedberg, A. S., and Lewis, H. D. (1944) *New Engl. J. Med.*, **231**, 731.

SEPTICAEMIA AND BACTERIAEMIA

See also B. E. M. P., Vol. XI, p. 76, and Cumulative Supplement, Key No. 1395.

Clinical consequences of a bacteriaemia

Septicaemia

Bacteroides infections—Smith and Ropes describe the clinical aspects of infections of Gram negative anaerobic non-spore bearing bacilli grouped together as bacteroides. The analysis is based on a review of the literature and a study of 20 cases occurring in Massachusetts General Hospital within 4 months. The organisms are common inhabitants of mucous membranes, particularly of the nasopharynx, the gastro-intestinal tract and the cervix and vagina, they may invade the tissues, the blood or the body cavities by extension of local inflammatory processes. Metastatic abscesses may occur in the lungs, pleural cavities, liver and joints. Bacteroides infections usually occur after throat infections, otitis media and mastoiditis, infections of the colon or genito-urinary tract, war wounds, and surgery of the large bowel. The septicaemias may be divided into 2 groups, as follows: (1) Cases caused by *Bacteroides funduliformis* which are pleomorphic bacilli with formation of large bodies (spheres) and filaments on cultivation in artificial media. In these cases metastatic abscesses often develop and the rate of mortality is high. Pus from the abscesses is thick, greenish yellow and foul, but not putrid. (2) Cases caused by *Bacteroides fragilis* or other non-pleomorphic bacteroides, such cases are less fulminating, show less tendency to metastasis and in them the prognosis is less grave. An epidemic of bacteroides septicaemias occurred in a group of soldiers with gunshot wounds, suggesting the implantation of particularly virulent strains, and indicates the desirability of isolating recognized cases occurring in hospitals containing wounded men. Treatment consists chiefly in surgical and supportive measures. Animal experiments indicate that sulphonamides may be of value, but clinical evidence is not conclusive.

Smith, W. E., and Ropes, Marion W. (1945) *New Engl. J. Med.*, **232**, 31.

SEX HORMONES

See also B. E. M. P., Vol. XI, p. 90, and Cumulative Supplement, Key Nos. 1396-1398.

Source and constitution

Anterior pituitary hormones

Animal experiments on anterior lobe—Young discusses animal experiments on the anterior lobe of the hypophysis and the application to man of the results of these investigations. Removal of the hypophysis does not cause death and does not induce obesity unless hypothalamic tissues are damaged. The outstanding morphological effects of removal of the anterior lobe include cessation of growth in the young animal and cachexia in the adult. Other effects consist of atrophy of thyroid gland, suprarenal cortex and reproductive organs with hypotrophy of the abdominal viscera. The appetite is diminished and there is a fall in the basal metabolic rate. Hypoglycaemia may develop during a short period of starvation, an increase occurs in the sensitivity to the hypoglycaemic action of insulin, and the diabetes mellitus due to pancreatectomy becomes less intense. The two pituitary gonadotrophins—follicle stimulating hormone and interstitial cell stimulating hormone—stimulate ovulation and corpus luteum formation. A third pituitary hormone, the so called lactogenic hormone (prolactin), may be necessary in order that the luteal tissue may be capable of elaborating

progesterone. The gonadotrophic substance of pregnancy urine is not identical with that of the hypophysis, but a positive Aschheim-Zondek test depends upon its presence. Three other substances have been separated from the anterior lobe. These are thyrotrophin, adrenocorticotrophin and a growth hormone. It is conceivable that one or more large molecules are secreted and that these may fragment to produce a variety of syndromes. In experimental chronic under nutrition a general depression of endocrine activity may develop in which anterior pituitary extracts can restore the depressed glands despite continuation of under-feeding. This state of pseudohypophysectomy may be related to the dysfunctions resulting from anorexia nervosa. Inhibition of oxidation may constitute the common metabolic change underlying the protean effects which are caused by the administration of extract of the anterior lobe of the hypophysis.

Effect on lymphocytes.—Dougherty and White present experimental evidence that pituitary adrenotrophic hormone influences the regulation of the number of blood lymphocytes. Diurnal variations in the blood picture of control laboratory animals was first ascertained. It was found that after injection of pituitary adrenotrophic hormone solution into mice there was a decrease in the total leucocyte count and in the absolute number of lymphocytes and an increase in the total number of polymorphonuclear cells. Maximum lymphopenic effect occurred 9 hours after injection, although shortly afterwards the leucocyte picture tended to return to the normal. There was an increase in haemoglobin and erythrocytes within 3–6 hours, and then a fall to subnormal levels which persisted up to 24 hours. Further experiments showed a correlation between the lymphopenia and a drop in adrenal cholesterol level. Injection of adrenotrophic hormone into rats and rabbits produced blood changes as in mice. The larger animals received less hormone per unit of body weight than did the mice, but they showed more lasting and profound effects. Adrenotrophic hormone does not produce leucopenia or lymphopenia in adrenalectomized animals, although there is an increase in the polymorphonuclear cells such as occurs in the injected intact mouse. Further experiments showed that the blood changes are not due to the protein nature of the hormone. Injections of pituitary adrenotrophic hormone in 2 hypophysectomized rats produced a decrease of about 5,000 lymphocytes within 8 hours. A similar effect is seen in adrenalectomized rats and mice which are given adrenal cortical extract. Aqueous adrenal cortical extract injected into mice produced extreme lymphopenia within 3 hours with polymorphonuclear leucocytosis. In adrenalectomized mice it gave blood changes indistinguishable from those seen in unoperated animals. In intact mice it showed decreases in haemoglobin and erythrocytes, but there were no initial increases noted in these constituents. Subcutaneous injections of adrenal cortical extract in certain hospital patients gave a tendency towards a decrease in erythrocytes, haemoglobin and lymphocytes, although the response was not as consistent as it was in other species.

Use of sex hormones in the treatment of menstrual and climacteric disorders

Physiology and disorders of menstruation

Oral administration of methyl testosterone in premenstrual distress.—Freed considers the treatment of premenstrual distress. Symptoms vary in character and in intensity, the commonest being headache, nervousness, emotional instability and depression. The most usual physical signs are bloating of the abdomen and subcutaneous oedema, and any existing lesion or disability may be aggravated. Different reactions may result from a single metabolic change, the sex steroids causing a retention of sodium with increase of extracellular fluid. Administration of ammonium chloride reduces the amount of sodium retention and satisfactorily relieves the symptoms. About 40 per cent of women suffer from some form of premenstrual distress which may prove to be a source of much disharmony in social relationships. As some success has been reported from the administration of androgens, these have been tested in 2 groups, each consisting of 30 private patients with premenstrual symptoms of distress. One group received 10 or 25 milligrams of testosterone propionate injected on the tenth and third days preceding the expected menses, the other group receiving 10 milligrams of methyl testosterone by the mouth daily, 10–7 days before the expected period. Both groups were relieved of most of their symptoms which are believed to be caused by increased secretion of oestrogen. Both progesterone and androgen have been shown to be effective in relieving symptoms of premenstrual distress. It is believed that vitamin B deficiency leads to impairment of the liver's function of destroying oestrogen, resulting in high tissue levels of oestrogen and thus causing the symptoms. The most effective treatment is the oral administration of methyl testosterone.

Gynaecology and obstetrics

Comparison of sex hormones used.—Gough discusses the value of sex hormones in gynaecology and obstetrics. Much is now known concerning oestrin and progestin, the hormones produced by the ovaries. Synthetic progestin (stilboestrol) is much more powerful and much less expensive than is oestrin. The ovarian hormones are controlled by prolans A and B, hormones derived from the hypophysis; two other less well understood hormones are found in the urine and serum of pregnant animals. The practical results of treatment with the sex hormones is often disappointing, partly because of the complexity of the relations of the sex hormones. In primary amenorrhoea not due to some serious disease, and provided the patient has a uterus, 1 milligram of stilboestrol may be given twice daily for 3 weeks, and then a few doses of progestin, 5 milligrams twice a week. This may produce menstruation

once or twice, but the effect is not permanent. In secondary amenorrhoea due to precocious menopause, or after childbirth, the treatment is more successful. In scanty menstruation, dysmenorrhoea and sterility a course of stilboestrol may be given with advantage. Uterine haemorrhages, in the absence of any gross organic disease, are usually due to an excess of oestrin and a deficiency of progestin, but treatment with progestin is very expensive and usually disappointing. Stilboestrol may be given with success in menopausal conditions, 1 milligram twice daily to begin with, the dose should be reduced as the symptoms decrease, flushes being a good guide to reduction. Overtreatment must be guarded against. The use of pituitrin (pituitary extract) as a very useful stimulant of uterine contraction is mentioned. Threatened abortion may be treated by administration of wheat-germ oil and progestin. The secretion of milk may be prevented by giving 5 milligrams of stilboestrol thrice daily for 2 days, after which the dose should be quickly reduced.

Clinical use of male sex hormone

Preparations of male sex hormone

Testosterone—Morgan states that Berthold in 1849 was the first to give scientific proof that the gonads have a profound influence on physical and mental development. Berthold demonstrated that castration of male animals produced deleterious effects on the sexual organs. It was found that the deficiencies could be removed by grafting testicular tissue into castrated animals. Potent extracts of testicular tissue, termed androgens, are now employed instead of grafts. Testosterone is the natural hormone of the testicle, and the chief urinary androgens which are derived from it are the 17-ketosteroids, androsterone and dehydroandrosterone. The 17-ketosteroids are also excreted in cases of hyperplasia or neoplasm of the suprarenal cortex. The action of testosterone propionate is somewhat transient unless the hormone is given by intramuscular injection in the form of a solution in a vegetable oil. Alternatively, compressed crystalline tablets may be implanted in the subcutaneous tissue in doses ranging from 50 to 100 milligrams. Methyl testosterone is excreted more slowly than is testosterone propionate, and is given in doses of 15–100 milligrams. The maximum effect is obtained if the drug is absorbed from the sublingual mucosa. In eunuchoids and castrates the continued administration of these hormones induces growth of the sexual organs and at least partial return of some of the secondary sex characters. Testosterone causes descent of the testes in certain cases of cryptorchidism, but the therapeutic value is limited by the ill effects, which include depression of spermatogenesis, priapism, excessive genital growth and acne of the face. In cases of delayed puberty it is better to try the effect of a gonadotrophic preparation before testosterone is used. It is doubtful whether testosterone is effective in the treatment of psychogenic impotence, sterility or prostatic hypertrophy, and the use of the hormone in gynaecology has not yet passed the experimental stage.

Therapeutic uses

Tests made with various steroids—Frame, Fleischmann and Wilkins present the results of administration of 11 different androgenic steroids to dwarfed, sexually retarded boys, as they had very low urinary 17 ketosteroids before treatment. The possibility of endogenous production of 17 ketosteroids obscuring the effect of steroid administration was minimal. The boys were in hospital during the study and received a diet of constant protein, carbohydrate and fat content. At varying intervals before and during treatment the total neutral ketonic 17 ketosteroids of 24-hour urine collections were estimated, both the administered steroids and the urinary 17 ketosteroids being calculated as androsterone. Administration of 6 steroids was accompanied by significantly increased excretion of 17-ketosteroids. Androsterone, dehydroisoandrosterone and Δ^4 androstenedione (3/17) are 17 ketosteroids. Of 20 milligrams administered per 24 hours about 30 per cent is recovered between the eighth and the fourteenth day, indicating that a portion of these compounds is excreted in a form similar in structure to that administered. Testosterone, free or as the propionate, Δ^4 -androstenediol (3 β /17a)-diacetate and androstenediol (3a/17a)-diacetate possess a free or esterified hydroxyl group in the 17 position. The fact that between 18 and 69 per cent of these compounds is recovered in the urine as 17-ketosteroids indicates that the body is capable of hydrolyzing the esters and of oxidizing the 17 hydroxy compound to a 17 keto compound. The compounds 17 methyl testosterone, 17 methyl Δ^4 -androstenediol (3 β /17a), 17-methylandrostenediol (3a/17a) and 17-ethyltestosterone each contain at C atom 17 the grouping HO—C—R, where R represents a methyl or ethyl group. After administration little if any of these steroids the metabolism of these compounds is not the removal of the alkyl group at C atom 17. For this reason the 17-alkyl androgenic steroids are valuable agents in the study of the effects of androgen administration on the endogenous production of urinary 17-ketosteroids.

General therapeutics

Hormones and the reproductive glands

Experiments on testes of ring-doves—Lahr and Riddle describe the changes in the testes of adult ring-doves after the birds had received injections of steroid hormones and other substances. A preliminary biopsy was performed for the purpose of estimating the weight of the testes. Daily injections were given for 10–14 days and the birds were then killed in order to ascertain the final weight of the testes. Sesame oil was used both as a solvent and as a control. In some cases the method of injection was supplemented by implanting a pellet of hormone subdermally. Atrophy of the testes occurred after injections of oestrone, oestradiol benzoate,

stilboestrol, desoxycorticosterone acetate (desoxycortone) and prolactin. The final weights of the testes varied from 14 to 22 per cent of the weights prior to treatment. Histological examination showed profound atrophy of the testicular germinal epithelium. Presumably this was the result of the ability of the hormones to inhibit the release of the follicle-stimulating factor from the hypophysis. Progesterone had a less pronounced effect on the testes but the action of this hormone resembled that of desoxycorticosterone acetate and prolactin in causing an increase in body weight. Oestrone was the only substance which had a slightly adverse effect on the body weight. Androsterone caused an increase in the weight of the testes by amounts varying from 23 to 39 per cent. Cholesterol did not produce any effect, but injections of phenol resulted in damage to the Leydig cells and a slight reduction in the weight of the testes.

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SHOCK AND COLLAPSE

See also B.E.M.P., Vol. XI, p. 126; and Cumulative Supplement, Key No. 1400.

Definitions and aetiology

Classification of shock

Review of main types.—Dunphy defines shock as “a state of actual or impending peripheral circulatory failure due to a reduction of the effective blood-volume which is not primarily cardiac in origin”. Shock can be classified although, owing to its complex and variable mechanism, its nature is still uncertain. (1) There is a neurogenic type caused by extreme mental stimuli or by pain, which gives rise to a state of widespread vasodilatation without primary capillary injury. (2) In vasogenic shock, of which histamine intoxication is the classical example, toxic action damages the capillary wall and causes it to lose constrictor tone; thus actual loss of fluid from the circulation is induced. (3) There is haematogenic shock, which is due to a primary loss of fluid from the circulation. (4) There is, too, a decompensation shock (so-called), which is the result of prolonged reduction of blood volume from whatever cause. Not only may one type lead to another and progress eventually to decompensated shock, but in any given patient more than one type may be the initiating factor. The parts played by the suprarenal gland, capillary injury and toxæmia in the production of shock are still indefinite. In the recognition of the various stages of the condition and in the assessment of the indications for and effects of treatment, chief reliance must still be placed on experience and sound clinical judgment, although laboratory aids are valuable. Morphine is of unquestionable value if it is given for the purpose of relieving pain, but the term, prevention of exposure, should be substituted for the time-honoured term, application of heat, in the treatment of shock. The adoption of the Trendelenburg position is efficacious in cases of vasogenic shock as well as in the haematogenic type until the blood volume has been restored—although maintenance of the blood volume by transfusion of blood or plasma as the situation demands is the real primary consideration in the latter type.

Hypotheses of shock

Toxæmia

Lipid depletion.—In recent years much attention has been paid to the possible part played by suprarenal glands in the production of shock, because of the many similarities between suprarenal insufficiency and traumatic shock. Popják records results of experimental shock produced in anaesthetized rats by binding rubber bands tightly around one hind limb, with resulting muscle necrosis. Twenty-four hours after release of the tourniquet the suprarenals showed a 31–42 per cent increase in weight and a significant increase in water content. Most of the increase in weight was due to the building up of additional cytoplasm. Frozen sections showed a marked reduction of stainable lipid, but 48 hours after injury the glands again contained a normal amount demonstrable both histologically and chemically. The lipid depletion was shown to be due to loss of ester cholesterol. Although there is as yet no direct evidence, it has been thought that adrenal cholesterol is a precursor of the adrenocortical hormones. It is known that lipid depletion of the suprarenals occurs in human subjects after surgical operations and in various infections, and that large amounts of adrenocortical hormone appear in the urine. Previous experiments have also shown a marked decrease in the cholesterol content of the suprarenals of rats after the injection of pituitary adrenocorticotrophic hormone. Popják considers that the available evidence tends to support the view that cholesterol is a precursor of the adrenocortical hormones and that its rapid disappearance from the gland under various conditions is due to its being converted into corticosterone or other related hormones.

Experiments on dogs.—Chess, Chess and Cole in experimental work eliminated the influence of anaesthetics and of nervous impulses in the production of shock by tourniquet constriction in order to estimate the evidence of the real cause of shock. Under anaesthesia, a preliminary

complete spinal cord section was made on 10 dogs at the level of the 12th dorsal or 1st lumbar vertebra. After 3 or 4 days when the dogs had recovered from the anaesthetic, rubber tubing was wound tightly around the thigh of the left hind limb and was prevented from slipping by a nail driven into the femoral trochanter. Tourniquet pressure was maintained for not less than 9 hours, when it was released. All dogs rapidly went into a state of shock and died. Blood pressure was determined before release of constriction and periodically after release by means of an intra arterial sphygmomanometer in the femoral artery of the right limb. The only sign common to all methods of elucidating causation of shock is a sustained fall in blood pressure. The dogs appeared to be normal, except for the effects of spinal cord section, during the period of tourniquet constriction, the blood pressure was normal. On release of the tourniquet, all dogs became restless and within 15 minutes the blood pressure fell 10–20 millimetres of mercury, rose again slightly and subsequently fell until death occurred at an average of 2–2½ hours after the release of the tourniquet. The amount of plasma lost into the dog's hind limb was estimated at only 2.1 per cent of body weight and cannot be the cause of death. Blood transfused from the constricted limb into another dog caused death 2–12 hours after the transfusion was started. The nature of the toxin elaborated in the constricted limb is not determined as either katabolic or bacterial in origin.

Discussion of aetiological factors

Many theories have been advanced in an attempt to explain the pathology of shock. Cope defines the process as a condition resulting from the application of harmful stimuli or the rapid depletion of body fluids, in which there is a serious and clinically demonstrable depression of the vital processes of the body, particularly of the circulation. Vasodilatation and transudation of fluid are two essential factors which are responsible for the gross diminution in the volume of blood in effective circulation, and the clinician constantly sees patients with shock due to severe loss of fluids, as in the case of haemorrhage. An ineffective response to treatment may be due to the constant transudation from the vessels or to the failure of the vasomotor centre to maintain intravascular pressure. Starling suggests that immediate shock is due to a nervous reflex which produces vasodilatation in the circulation in the flaccid muscles. Shock is produced rapidly by toxins which are absorbed after the relief of obstruction of the small gut, the effect of toxins is also demonstrated by the observations of Green who obtained a substance from fresh voluntary muscle which reduces the blood pressure on intravenous injection. Changes in the pulse and skin are variable but a subnormal temperature and a persistent reduced blood pressure are important clinical features of shock. The prognosis is grave when the systolic pressure falls below 80 millimetres of mercury, and a pulse pressure lower than 25 millimetres is particularly serious. Latent shock may be present however, even while the blood pressure remains high.

Treatment

Gelatin solution

Blood reactions—Jacobson and Smyth describe the administration of gelatin to human beings as a substitute for plasma. A 5 per cent solution of purified bovine osseous gelatin was given intravenously to 45 healthy individuals in 3 moribund cases and in 50 cases of shock. Between 450 and 1,000 cubic centimetres were given at each injection, the total number of injections varied. In 12 cases the increase in plasma volume and the rate of disappearance of the gelatin from the blood was measured. In all cases an appreciable increase in the plasma volume lasting for at least 24 hours was recorded, whereas after 4 hours 80 per cent and after 24 hours 87 per cent of the gelatin had disappeared. Examination of the urine in 5 cases showed excretion of 46 per cent total gelatin in 4 hours and 76 per cent in 24 hours. No significant changes occurred in the blood urea, nitrogen, and amino acid levels in 15 cases in 24 hours after injection but in 12 cases in which tests were made the erythrocyte sedimentation rate showed a rise parallel to the concentration of the gelatin in the serum, becoming approximately normal at 24 hours. Necropsy performed on the patients who died showed no tissue changes attributable to the gelatin. The 50 patients with shock gave a good clinical response to the gelatin therapy. No allergic or other unfavourable responses were recorded. From this preliminary survey the authors can find no evidence that metabolism of gelatin occurs after injection and believe that it should be given a full clinical trial as a substitute for plasma in the treatment of shock.

Effect on vascular system—Before a blood substitute can be accepted as a therapeutic agent it must be shown not to produce any permanent pathological changes after repeated administration. Morehead and Little gave gelatin solutions to 9 dogs in concentrations similar to those used clinically. The animals were given 12 daily intravenous injections—each equivalent to 1 per cent of the body weight—of either 6 or 4 per cent gelatin in aqueous 0.9 per cent sodium chloride solution, and were sacrificed after varying periods of time for post mortem study. Except in one dog the pathological findings were confined to the aorta, kidneys and coronary arteries. In the aorta nodular thickenings composed of delicate elastic lamellae and fibrous tissue, in the intima of the abdominal portion, were the most common findings. Degenerative changes in the elastic tissue of the media, confined for the most part to the ascending aorta and arch, were found in nearly all the dogs and some showed degeneration of elastic tissue and collagen resulting in cyst formation. In one animal, aortic bacterial endocarditis associated with *Dirofilaria immitis* was found, a typical focal nephritis was

present as well. In only one dog was a lesion, consisting of a localized thickening of subendothelial connective tissue of the intima, seen in the coronary arteries. Five of the animals showed chronic interstitial nephritis but since this is a common finding in dogs it was without significance. The authors point out that the lesions found were, in general, those of vascular degeneration and repair and that if they had resulted from the gelatin some correlation, which was not, in fact, noted, would have existed between them and the duration of the experiments. They state that it is not generally recognized that spontaneous aortic disease occurs in dogs, a fact which they have demonstrated by study of healthy control animals. Lesions could be seen which did not differ from those recorded in the above experiments with gelatin.

Report of 52 cases.—Kozoll and his colleagues studied the effect of gelatin in the treatment of 52 patients with shock, who received an intravenous infusion of 1,000 cubic centimetres of a 5 per cent solution of gelatin in physiological saline. It was found that this was a safe procedure and that shock was relieved in most cases without any additional treatment. No untoward reactions occurred except in a case of abdominal carcinomatosis in which the temperature rose by 3° F. during the infusion. The pyrexia was considered to be due to the underlying disease. An improvement in the character of the pulse was noted and, in those patients that responded to treatment, the cool clammy skin became warm and dry. The blood pressure rose in all but 2 cases and remained at the normal level after completion of treatment. One patient with surgical shock required a second litre of gelatin before relief was obtained, but a total of 5,000 cubic centimetres was unsuccessful in a patient with diabetes mellitus and burns. Both plasma and gelatin failed to prevent a fatal outcome in a case of intestinal obstruction. In 2 cases blood and plasma transfusions were successful after gelatin had failed. Four patients were relieved by gelatin but died later of other causes. In all probability gelatin solution is an effective agent because it produces dilution of blood. The dilution of the plasma protein is not necessarily disadvantageous since significance is attached to the total amount of plasma protein but not to the concentration. The only undesirable effect resulting from the use of the method is an increased sedimentation rate due to rouleau formation (pseudo-agglutination). If the number of erythrocytes is reduced before the commencement of treatment, as in cases of severe haemorrhage, a further reduction is dangerous.

In severe shock.—Evans and Rafal record the results of the clinical use of gelatin as a blood or plasma substitute in the initial treatment of severe shock resulting from trauma of extremities, chest and abdomen in 67 patients and after severe burns in 28 other patients. The gelatin must be specially prepared for intravenous therapy and, when made available for general use, it will have to comply with specific requirements. The effectiveness of any blood substitute depends upon the length of time it remains in the circulation, a period which, in turn, depends upon the molecular size of the substitute. Two types of gelatin were tested for retention in the circulation, heavily degraded and lightly degraded. The heavily degraded type leaves the circulation rapidly whereas the lightly degraded is found in the circulation 8 hours after rapid infusion. The lightly degraded type was used in the treatment described. In traumatic cases of shock is due mainly to loss in blood volume and in these cases 1,000 cubic centimetres of 6 per cent gelatin solution in 0.85 per cent saline are administered intravenously by the rapid syringe technique, which permits the swift restoration of the blood pressure. In cases with less blood loss 500 cubic centimetres are given rapidly, and another 500 cubic centimetres slowly during operation. Experience with gelatin in the management of burn shock has proved to be satisfactory. In children it is administered in the first 24–36 hour period at intervals of 4–6 hours in fairly large infusions, preventing death from burn shock. If the burn is superficial and widespread large infusions are given during the shock period. In the absence of blood or plasma stocks, gelatin will be a ready means for initial treatment in emergency but, although it is less expensive, it can never be a true substitute for whole blood therapy.

Gelatin and pectin

Popper and his collaborators consider that solutions of gelatin or of pectin are effective substitutes for plasma in the treatment of shock. Gelatin in 5 per cent solution was injected intravenously in 162 patients, and the quantity administered ranged from 1 to 10 litres per patient. A similar procedure was adopted with pectin in 0.9 per cent solution of sodium chloride. About 50 per cent of the persons treated were suffering from shock, and it was in these cases that the 2 solutions caused the greatest haemodilution. In every instance, however, the level of haemodilution was diminished when the amount of solution injected exceeded 1,000 cubic centimetres. This change was especially noticeable in patients with anaemia and hypoproteinaemia. The two substances caused a uniform rise in the sedimentation rate of the erythrocytes. In 3 cases necropsy showed that the gelatin injections had produced vacuolation of the epithelial cells of the renal tubules. The changes due to pectin consisted of dilatation of the tubules and of the glomerular spaces. Furthermore, high dosage of pectin resulted in splenomegaly, proliferation of the reticulo-endothelial cells, and the deposition of a peculiar material in various organs, including the spleen, liver, kidneys and lungs. Histologically, the picture resembled amyloidosis. The staining reactions, however, proved that the material was pectin and not amyloid. Similar results were obtained in experiments on animals. It is concluded that gelatin solution is the preparation of choice in the treatment of shock, since pectin produces a greater degree of tissue damage.

Plasma protein

The protein pool—Whipple and Madden discuss the interchange and construction of haemoglobin, plasma protein and cell protein in emergencies. There is a dynamic equilibrium between plasma protein and cell protein, and the former given intravenously can supply all the protein requirements of the body. Experiments on dogs have shown that the animals can be maintained in health, weight and a positive nitrogen balance for weeks when receiving carbohydrates, fat, minerals, and accessories given by the mouth and plasma protein as plasma administered by vein. The albumin globulin ratio was little changed by long-continued daily plasma injections, showing that all plasma proteins are freely used. The liver appears to be the master organ for protein metabolism, owing to its size and strategic situation. Fibrinogen and prothrombin come from hepatic epithelium and evidence is accumulating to prove that albumins, and probably some of the globulins, come from the liver. Dogs on protein free diet and subject to frequent bleedings, when given various proteins and protein digests quickly manufactured new haemoglobin and plasma proteins. Dog haemoglobin given into the peritoneal cavity in large quantities did not cause haemoglobinuria but produced new haemoglobin and plasma protein. Haemoglobin and casein digests are well used when given by vein. The doubly depleted dogs can also use whole plasma and, to a large extent, plasma digests, in order to produce much new haemoglobin, and the 10 amino-acids necessary for growth are also very effective. These experiments have an important bearing on the clinical treatment of shock and postoperative conditions. Digests and amino-acid mixtures should be given as well as plasma, and are effective when administered by vein, subcutaneously, intraperitoneally, or by the mouth. From these experiments the concept of a large protein pool emerges, from which haemoglobin, new plasma protein, or cell protein may be derived according to need, the medium of exchange being the circulating plasma protein.

Serum albumin

Report of a series of patients treated intravenously—Cournand and his colleagues report favourably on the use of intravenous injections of concentrated human serum albumin in the treatment of 12 patients who were in a condition of acute traumatic shock. In 9 instances the preparation consisted of 25 grammes of albumin in 100 cubic centimetres of saline. Sodium acetate was added in some cases but this did not appear to have any additional effect on the retention of albumin in the circulation. The data showed that the serum protein concentrations tended to remain about the same before and after the injections. The albumin was largely retained provided that no further bleeding or exudation of plasma occurred. On the average, 9 patients received 62 grammes of albumin and retained 43 grammes. The average amount of increase in blood volume per gramme of albumin retained was 23 cubic centimetres. This increase was still maintained after a period of observation of 6 hours. A great improvement in the circulation resulted and all the primary changes associated with recovery from acute shock were observed, including increase in right atrial pressure, arterial pressure and cardiac output. Six patients were treated with rapid intravenous infusions of saline but the degree of improvement in the circulation was comparatively small and was less sustained. Patients treated with serum albumin were found to have a greater rise in cardiac output than had those given transfusions of whole blood. In shock due to skeletal trauma or haemorrhage, however, haemodilution and reduction in blood volume require whole blood for the purpose of increasing the blood flow and the amount of haemoglobin. The results of the investigation indicate that whole blood should be given when acute anaemia persists after albumin therapy. In cases of shock with severe dehydration, the giving of concentrated albumin is not harmful to patients but treatment is more effective if water and salt are also administered.

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SILICOSIS

See also B. E. M. P., Vol. XI, p. 133, and Cumulative Supplement, Key No. 1401.

Aetiology*Incidence and susceptibility*

Results in experimental silicosis—Haythorn and Taylor describe experiments in which rabbits were given intravenous injections of crystalline silica. Perivascular phagocytes and

silica nodules were produced. In one rabbit cirrhosis of the liver developed. Intraperitoneal injections of silica into guineapigs resulted in areas of necrosis, adhesions, and calcified nodules in the liver, spleen and lymphatic glands. Similar results were obtained by injecting animals with suspensions of lung ash from a case of massive silicosis. Other rabbits and guineapigs were injected with the lung ash of a case of bronchogenic carcinoma. The dust was free from silica and contained a small amount of total silicates. No gross lesions developed and all the animals survived. The guineapigs were found to have collections of phagocytes and foreign-body giant cells containing brown pigment. Almost all these cells were beneath the peritoneum. The results were typical of the absorptive reaction of Miller and Sayers. Mixed dusts containing free silica were recovered from the lungs in 2 cases of silicotuberculosis. Injections of these dusts into animals produced in some instances pronounced absorptive lesions without fibrosis. Apparently the silicates and other contaminating dusts protected the animals from the toxic action of the silica.

Treatment

Aluminium therapy

Experiments with guineapigs.—Gardner, Dworski and Delahant discuss aluminium therapy in silicosis. After a long series of experiments on guineapigs they conclude that silicosis will not occur if gelatinous alumina and quartz are introduced into the animal body separately, provided that both substances lodge in the same phagocytic cells. Furthermore, alumina injections will resolve immature silicotic lesions and will prevent further enlargement of fibrous nodules. The alumina is apparently harmless and in small doses will not increase susceptibility to tuberculosis although excessive doses, by the blocking of the phagocytic defence mechanism, may lead to progression of the disease. When the authors tested the relative efficiencies of powdered aluminium and its colloidal hydroxide they found that the metal did not disperse but remained at the site of injection, silicosis occurring in other parts of the body, whereas the hydroxide was stable and dispersed freely throughout the body. The best method of administration appeared to be an inhalation of dried powdered aluminium hydroxide. Groups of guineapigs were exposed to this suspension for varying lengths of time in a quartz-laden atmosphere. No silicosis occurred over a period of 17 months, but there was so much non-specific reaction that Gardner and his colleagues cannot recommend the safe use of the preparation as an inhibitor. A different preparation is now undergoing trial and so far results appear to be more favourable. Guineapigs with a mild tuberculous infection showed a spread of foci when first exposed to the effects of hydrated Alumina XH-1010, but later healing occurred without destruction of the tissue. So far the authors have little experience of the effect of aluminium on human beings with silicosis. The patients treated did not cooperate well on the whole and would not persist with treatment, but in the 2 who did cooperate there was marked improvement. The authors conclude that aluminium therapy deserves clinical trial, although it should not replace methods of dust control.

Gardner, L. U., Dworski, M., and Delahant, A. B. (1944) *J. industr. Hyg.*, 26, 211.

Haythorn, S. R., and Taylor, F. A. (1945) *Amer. J. Path.*, 21, 123.

SIMMONDS'S SYNDROME

See also B.E.M.P., Vol. XI, p. 145.

Treatment

Male sex hormones

Use of testosterone.—Burke and Cantor review the observations of earlier workers that some patients with Addison's disease, although in receipt of adequate amounts of desoxycorticosterone, continue to lack energy. A gain in weight and strength can be produced by administering testosterone propionate which appears to give a positive nitrogen balance. The knowledge has been applied to dwarfism of pituitary origin with the same beneficial result and to Simmonds's disease in which hypophyseal function is destroyed by intrasellar tumours and in which the results of treatment with extracts of whole anterior pituitary substance have proved disappointing. The authors report on the successful treatment with testosterone propionate and methyl testosterone used concomitantly. The patient was a male, with functional Simmonds's disease, in whom all the criteria of the syndrome were present except alteration in the character and distribution of pubic and axillary hair and in whom there was not a clinically demonstrable pituitary lesion. In less than 2 months of hospital treatment the patient's weight increased from 94 to 110 pounds and, a few months later, to 145 pounds. The patient was able to return to work, and the blood pressure, pulse and metabolic rate became normal. Previously the blood pressure had been 94/66, pulse rate 46, and basal metabolic rate -24. Lost libido was recovered.

Burke, G., and Cantor, M. M. (1945) *Canad. med. Ass. J.*, 52, 275.

SKIN DISEASES: AFFECTIONS DUE TO INSECTS AND ACARINES

See also B.E.M.P., Vol. XI, p. 149; and Cumulative Supplement, Key Nos. 1403 and 1404.

Parasites breeding on human host

Pediculus capitis

Treatment by Lethane 384.—Scobbie states that many substances are lethal to the louse, but the insecticide with the quickest and most effective laboratory action is Lethane 384

11 cases of scabies after the application of about 50 cubic centimetres of the solution. No patient experienced any ill effects due to the use of Synl.

Eddy, G. W. (1944) *War Med.*, 6, 319.

Gordon, R. M., and Unsworth, K. (1944) *Ann. trop. Med. Parasit.*, 38, 207.

Mellanby, K. (1945) *Brit. med. J.*, 1, 38.

Scobbie, Elizabeth B. S. (1945) *Brit. med. J.*, 1, 409.

SKIN DISEASES: OCCUPATIONAL DISEASES

See also B.E.M.P., Vol. XI, p. 161; and Cumulative Supplement, Key Nos. 1405-1408.

Dermatitis

Causes

Cutting oils.—Whitwell states that not all cutting oils are equally harmful in causing dermatitis. This fact cannot be correlated with any physical property of the oils. The thick heavy cutting oils do not necessarily produce the most oil acne although, in theory, these liquids should block the pores most readily. A hairy skin predisposes to folliculitis, but seborrhoea, unaccompanied by acne vulgaris, appears to confer a large amount of immunity to trade dermatitis. Some thick medicinal greases derived from petroleum never give rise to acne. Folliculitis often occurs, however, with ointments consisting of petroleum jelly mixed with certain tars. During a period of 2 years the author saw no case of dermatitis or acne in people working with lubricating oil of good quality. In contrast, new cases of acne were seen daily in operators using the cruder cutting oils. No cases of oil rash have occurred in 5 years in a group of garages employing 140 men, but there was a small outbreak of dermatitis 6 years ago due to the use of paraffin and sawdust for cleansing purposes. Cutting oils should not be thinned with paraffin. Furthermore, chemical research could do much to make the oils less harmful.

Effects of tetryl.—Probst, Mund and Lewis report on a study of the effects of tetryl on about 900 workers in tetryl areas, most of whom were loaders although some were doing research work or were manufacturing tetryl. Skin irritation was a common complaint and 404 cases of tetryl dermatitis occurred. The face and neck were most commonly affected, and the dermatitis developed in new workers in from one to several weeks. Some allergic cases developed in a few moments after exposure. The typical contact dermatitis became papulovesicular and then brawny, resulting in scaling and discoloration of skin. No systemic reactions occurred, hearing and vision were not affected, and there were no corneal lesions. Subjects complained of nasal dryness, burning and sneezing, stuffiness and anosmia, often with epistaxis. Objectively a dry infected nasal mucosa was found with oedematous conchae, and the pharynx was dry, glazed and infected. Laryngitis and tracheitis were not caused by tetryl. Under appropriate treatment with 10 per cent boric acid ointment or 5 per cent sodium bicarbonate wet dressings, and removal from exposure, the dermatitis cleared up quickly. Every effort was made to reduce the incidence of affection by the exclusion from tetryl areas of all workers with any throat, nose or lung affection or with any serious systemic disability, by the use of anti-dust appliances and the provision of protective clothing and adequate washing and bathing facilities, with sufficient soap and towels, and by instruction of the workers in preventive and hygienic measures.

Fish.—Schwartz and Tabershaw discuss occupational dermatitis in the fish industry. Abrasions and lacerations are common throughout the industry, and secondary infections are often seen. Staphylococcal infection secondary to trauma from dirty oilskins is constantly seen on the wrist; the lesions are called "pigeons" by fishermen. Bites and stings occur from dogfish, sea anemones and rays. Redfeed dermatitis occurs from working with mackerel when they are in season and are feeding on "redfeed", a minute reddish orange crustacean; the dermatitis develops on the sides of the fingers and on the palms. Working with ungloved hands among skipjacks (a kind of mackerel) also in some cases causes dermatitis. Skin punctures from the bones of rosefish may cause lymphadenitis and suppuration. Erysipeloid occurs on the Atlantic coast chiefly in workers in contact with the remains of putrefying fish (fish-offal); *Erysipelothrix rhusiopathiae* has been demonstrated as the cause. Owing to exposure to excessive sunlight and tar used in ropes and nets an increased incidence of epitheliomata has been noted. Allergy to fish oils can also occur, usually among people who handle cooked fish. The authors state that dermatitis can be prevented by the wearing of rubber gloves thick enough to hinder the occurrence of punctures by bones and having treads on the fingers so that the handling of fish is facilitated. If a puncture is sustained from a rosefish bone or from gurry the wound should be made to bleed freely. Chlorine can be added in small amounts to water used for washing knives and gloves.

Probst, E. W., Mund, M. H., and Lewis, L. D. (1944) *J. Amer. med. Ass.*, 126, 424.

Schwartz, L., and Tabershaw, I. R. (1945) *J. industr. Hyg.*, 27, 27.

Whitwell, G. P. B. (1945) *Lancet*, 1, 529.

SKIN DISEASES: TUMOURS

See also B.E.M.P., Vol. XI, p. 200; and Cumulative Supplement, Key Nos. 1412-1415.

Innocent tumours

Derived from superficial layers of epithelium

Vaccines for warts.—Biberstein advocates injections of vaccines in the treatment of warts and

condylomata acuminata. Immunization therapy was founded on clinical and experimental investigations which had proved the infectious nature of the lesions. The vaccines were prepared from material obtained from these lesions and ground to a pulpy consistency in a solution of sodium chloride. Bacteria and viruses were removed by sterilization of the mixture in a water bath at 56–60° C for 2 hours. Filtration through gauze removed particles which would not pass the needle and phenol was added in order to produce an antiseptic content of 0.5 per cent. The Berkefeld filter was used when sufficient material was available, as in the case of vaccines prepared from cattle warts. The vaccine was administered twice weekly and two injections, each of 0.1 cubic centimetre, were made intracutaneously each time. This procedure is based on experience in intracutaneous sensitization with sera. The author's first series of cases comprised 112 patients and 75 per cent of those who received more than 10 injections were influenced favourably. In a second series of 261 patients successes were obtained in 65.4 per cent of the cases of *verrucae vulgares*. Favourable results were also obtained in more than 85 per cent of the patients who had *condylomata* and *verrucae planae juveniles*. Seventy-one patients were given extract of cattle warts and the recovery rate in the various groups ranged from 56.5 to 90 per cent. The psychotherapeutic factor is excluded by the demonstration that the vaccine cures papillomatosis in cattle and horses. The method is of particular value for patients with an excessive number of warts, especially when other forms of treatment have failed. Moreover, it may not be practicable or advisable to use methods other than vaccine therapy for warts in the subungual or plantar regions.

Derived from nerve tissue (glomus tumour)

Report of a multiple condition—Slepyan reports on the unusual occurrence of multiple painful and painless glomus tumours in the same patient. These abnormalities were manifested in a seaman, aged 34 years, who complained of a painful swelling on the right forearm. The swollen area was purple in colour and consisted of 2 freely movable discrete nodules 1 centimetre in diameter. Pressure on the nodules caused pain which radiated to the shoulder and to the fingertips. Scattered over the body were 12 smaller painless lesions coloured in varying shades of purplish blue. Two nodules had deep telangiectatic vessels over the central blue spot. In some of the larger tumours the patient experienced a burning sensation during sudden changes of temperature, especially in cold weather. Excision of the 2 painful tumours led to immediate alleviation of pain. In addition, a painless tumour was removed from the left arm and all 3 lesions were examined microscopically. The appearances were essentially those of a glomus tumour and a cavernous haemangioma but the epithelioid cell mantles were relatively less developed in the painless tumour. A considerable number of nerve elements surrounded and adjoined the vascular structures. The afferent arteries in the painless lesion were found to be immature and this may have accounted for the lack of pain, since the factor of pressure was absent. It has been suggested that these tumours are of the nature of telangiectases and it is concluded that the identity of painless glomus tumours can be determined only by microscopical examination.

Malignant tumours

Derived from superficial layers of epithelium

Prophylaxis of cutaneous cancer—In a Thom Bequest Lecture delivered before the Royal College of Surgeons, Edinburgh, Aitken deals with the prophylaxis of cutaneous cancer. Only a 0.11 per cent increase in the incidence of such cases has occurred during the past 10 years in the Skin Department of the Edinburgh Royal Infirmary, although apparently more early cases of rodent ulcer than formerly have been referred for treatment. The cause of rodent ulcer is unknown, but the lecturer had seen a case of ulcer between the eyebrows, occurring in a sailor, in which a history of injury was suggestive. Epithelioma may occur after injury or chronic irritation of the skin. Arsenic may act as an external irritant or may cause epithelioma when it is taken internally for long periods. Light heat and x rays, soot, tar, pitch, anthracene and paraffin are all causes in some instances. Most of the chemical causes occur as occupational hazards. Cancer of the scrotum is said to be eight times more common in chimney-sweeps than it is in the general population. Blast furnace tar does not produce cancer in either men or mice, but lignite, gas-workers' tar, producer gas tar and coke oven tar may produce it. Cancer, most often of the scrotum, is common in the cotton and shale-oil industries. In the former, mule-spinners are chiefly affected. Paraffin workers are prone to develop epithelioma of hands, forearms or scrotum. Baths, drying of soiled working clothes, the use of protective applications to the skin, and the weeding out of men who show a tendency to early paraffin eruptions have been found to be effective prophylactic measures in the Scottish Oil Works.

Melanotic carcinoma—Tod discusses the tragedy of malignant melanoma and describes its correct treatment. Although not a common tumour it is not very rare, 74 cases having been seen during the last three years at the Holt Radium Institute, Manchester. Of 100 cases treated between the years 1933 and 1942, 34 patients died as a direct result of incomplete or incompetent primary treatment. Very grave risks are run when a pigmented mole is treated by simple excision, by ligation or by cauterization only. It is never justifiable to remove for cosmetic reasons, except by radical operation, a pigmented lesion which shows no signs of growth, and even then only if the patient insists on its removal after being warned of the danger. If a suspected lesion is growing, radical excision or irradiation to the highest tolerable dose is necessary. A pigmented lesion with enlarged regional glands requires wide excision.

of both the primary lesion and the glands, with, if possible, the lymphatic vessels between. When metastases are present beyond the regional lymphatic glands, cure is impossible, but palliative irradiation may be tried. The results of cases treated at the Holt Radium Institute show success in 73 per cent of those patients whose primary treatment was radical, but only in 28 per cent of cases in which the first treatment was incomplete or unsuitable. It should be remembered that in most cases melanoma (the common mole) is entirely benign, and if it is left alone it will remain benign.

Derived from hair follicles

Sodium bicarbonate therapy in rodent ulcer.—In 1934 Cameron gave a lotion of bicarbonate of soda to a patient with an apparent basal-celled carcinoma with the object of removing sebaceous material in the ulcer. In a month's time the ulcer had disappeared. In another case of rodent ulcer similarly treated the ulcer disappeared in 9 days; 4 years later the patient returned with a rodent ulcer near, but not at the site of, the old one. Again the application of bicarbonate of soda caused its disappearance. In all, Cameron has treated 28 malignant growths of the face and neck by this method. Of 16 rodent ulcers verified by histological examination, the lesion disappeared in 8 and 4 have been healed for over 5 years. Bicarbonate of soda has been used in various strengths of solution in water, in lotions with glycerin and water and in pastes and ointments. Only malignant tissue is adversely affected. Bicarbonate of soda does not impair the effect of radium nor is it prejudiced by the previous use of radium. One case failed to respond to treatment with bicarbonate and was cured by application of interstitial radium. Another was healed when radium had been unsuccessful. Cameron suggests that the bicarbonate of soda may increase the osmotic pressure of the lymph bathing the cancer cells and thus damage them, or by altering the hydrogen ion concentration it may inhibit the action of some enzyme such as the proteolytic one which constitutes the "diffusion factor"; or it may remove a local carcinogenetic substance.

Rodent ulcer: radium therapy.—In 1940 Charteris described rapid radium implantation for rodent ulcer. In 76 patients there were only 2 failures. In the present communication he describes a modified method, compressed into 30 hours, used in 62 cases which included 3 of squamous epithelioma and 59 of rodent ulcer. In order to prevent sepsis, the skin was painted with 1 per cent proflavine oleate in liquid paraffin and was locally anaesthetized. The needles used were 15 millimetres long, had an active length of about 5 millimetres and 0.6 millimetre platinum walls and a radium content of 2 milligrams (element). The basic arrangement was a rectangular plane 2.5 × 1 centimetre in size, made of 6 needles. The implant was carried out 0.5 centimetre below the skin. The dose was 100 r per hour at presumed skin surface. During treatment the eye was not bandaged, and acriflavine drops were freely used. The treated area should be kept dry and covered with sterile sulphanilamide powder. With the new technique no eye damage has been observed in 5 cases in which the growth developed in the upper lid or in other cases in which the growth spread to the upper lid. Distance protection was obtained by a thick contact glass which raised the upper lid 0.5 centimetre, reducing the radiation on the globe by 50 per cent. The eyelid was stabilized by being stitched to the cheek. The cosmetic results were excellent. Three cases in this series were regarded as failures. After treatment epiphora developed in 3 cases. The reduction in the treatment time implied a lower dose; a skin dose of about 3,000 r in 30 hours appeared to answer well since it was effective without being the cause of excessive reaction.

Innocent infective conditions

Sarcoids

Report of three cases.—Stuart reports on 3 cases of sarcoidosis of Boeck. The aetiology of the condition remains obscure. The so-called hard tubercle is the typical pathological lesion and is a collection of large pale-staining polygonal epithelioid cells, about the size of a miliary tubercle. Although giant cells are common they are not always present. These tubercles are reported to remain unchanged for long periods; they may be found in all tissues, but most often in lymphoid tissues, and they heal by hyalinization and fibrosis. The signs and symptoms vary with localization and extent of the lesions. With diffuse pulmonary infiltration, dyspnoea and right heart failure may be found, and with Heerfordt's syndrome, failing vision, facial paralysis and parotid swelling. A leucopenia with relative monocytosis and eosinophilia are usually present. There may also be a reversal of the albumin-globulin ratio. For absolute diagnosis a biopsy of a lymph gland should be done. The 3 cases reported on were in a female aged 19 years and in males aged 16 and 17 years, all coloured. Pulmonary and lymph gland lesions were present in all. In 2, Heerfordt's syndrome was present; one had failing vision and in the other slit-lamp examination showed keratic precipitates. Leucopenia and relative eosinophilia were present in all. Skin lesions were present in only 1 case. Very full metabolic studies were made in all 3 cases. Guineapig inoculations with material from lymph glands from 2 cases were negative; serum alkaline phosphatase values were elevated in all 3. In one case the P-R interval (0.2 second) was prolonged, and though a rheumatic lesion could not be eliminated, the author suggests that the prolongation might have been due to sarcoid lesion of the heart. Stuart concludes that these investigations have supplied no further evidence regarding the aetiology of the condition.

Tumours of the scalp

Treatment

McNeill Love describes treatment of tumours of the scalp. For sebaceous cyst he recom-

mends simple transfexion with a bistoury, expression of contents and avulsion. When infection or ulceration has occurred dissection is advisable. Discussing moles, the author warns that ulceration, a tendency to bleed, induration or increase in size raise a grave suspicion of malignancy and he advocates wide excision. Lipomata of the scalp may be in either subcutaneous tissue or the fat in the loose areolar layer. Trouble due to size or position indicates operation. Cirsoid aneurysm is rare and difficult to treat. It is a pulsating, readily compressible swelling the overlying skin of which may show capillary naevi. It is due to dilatation of arteries opening more or less directly into venous spaces. As ultimate ulceration is likely to lead to fatal haemorrhage, extirpation in the early stages is indicated. Previous ligation of arteries at successive operations is sometimes necessary and should be done at short intervals so that collateral circulation may not be established. Rodent ulcer or basal-celled carcinoma has a raised and beaded but not everted edge. Small rodent ulcers should be excised, large ones should be treated with radium needles or plaques, 40-80 milligram-hours per square centimetre depending upon depth of ulcer. X-rays are required only when bone or cartilage is invaded. Surgical removal of part of the diseased tissue, in addition to radiotherapy, is advocated in advanced cases. Epithelioma the author treats with radiotherapy and excision and irradiation of regional glands. Secondary carcinoma of the skull may eventually involve the scalp. Palliative treatment only is possible.

Aitken, R. (1944) *Edinb med J*, 51, 339

Biberstein H (1944) *Arch Derm Syph*, N Y, 50, 12

Cameron, D (1944) *Lancet*, 2, 720

Charteris A A (1944) *Amer J Roentgenol*, 52, 423

Love, R J McN (1944) *Med Pr*, 212, 196

Slepyan, A H (1944) *Arch Derm Syph*, N Y, 50, 179

Stuart B M (1944) *Amer J med Sci*, 208, 717

Tod, Margaret C (1944) *Lancet*, 2, 532

SKIN DISEASES: GENERAL

Diagnosis

The electron microscope in dermatology

Clark and his colleagues state that an almost total vacuum is needed in the electron microscope, since air scatters electrons. Moist and living specimens cannot exist unchanged for long in such a vacuum. Moreover, the specimens must be exceedingly thin in order to allow adequate penetration by the electron beam. The electron microscope gives a magnification of nearly 30 000 diameters, and the image can be photographically enlarged to 125,000 diameters. There is no doubt that the use of the instrument will bring about advances in dermatology but, as yet examination of the skin has not yielded very encouraging results. The authors examined thin sheets of skin from the ear of an adult rat. The cell boundaries and nuclei were clearly distinguished and the detail was much sharper than that obtained with the optical microscope. Owing to limitations of penetration however, the detail became poor with the higher magnifications. In the course of a study of fixatives and stains Mudd's observations were confirmed in relation to the use of sodium bicarbonate. Cells were soaked for 24 hours in a solution of the salt. The cytoplasm was rendered extremely transparent by this method, and the granules stood out clearly. Electron micrographs of a cosmetic face powder showed particles which had the appearance of thin flakes piled one on top of another like the leaves of a book. Another brand of powder consisted of particles with sharp jagged hooks and spines. Such micrographs may prove to be of value in the study of cutaneous irritation due to cosmetics. Good results have been obtained from the examination of delicate animal tissues such as cockroach cuticle, mosquito egg cases and filaments of spider web. Other investigations have proved that chromosomes are fibrillar in nature, and that particles of influenza virus measure about 10 millimicrons in size.

Clark, G L, Baylor, Martha B, Martin Dorothy E, and Rafferty, Gertrude T
(1945) *Arch Derm Syph*, N Y, 51, 81

SMALLPOX

See also B E M P, Vol XI, p 269, and Cumulative Supplement, Key No 1416

Clinical picture

Smallpox in Egypt

Illingworth and Oliver describe 100 consecutive cases of smallpox seen in a military hospital in Egypt. Ninety five patients were soldiers, white and coloured, between the ages of 20 and 40, 4 were adult civilians and one was a baby. Of the 100 cases, 54 were of the mild modified type, with rapidly maturing rash, in 24, unmodified, the rash ran a normal course. 14 of these were mild and 10 severe. Twenty-two showed haemorrhagic manifestations, and of these 17 were severe. The case mortality was 14 per cent. It was found to be impossible in the early stages to diagnose modified smallpox from chickenpox, reliance on 3-4 day prodromal fever, commencement of rash on the extremities, centrifugal distribution or absence of cropping leading to serious error. Haemorrhagic cases in the early stages closely resembled measles, even to the presence of Koplik like buccal lesions. This resemblance has not been sufficiently emphasized. The examination of scrapings from pustules or vesicles for elementary bodies was of great assistance in diagnosis, and it is suggested that the test should become a routine. All but 4 of the patients had been successfully vaccinated, 70 within 2 years and most of them

period Unilateral sciatica was present in all but 2 of the cases, and pressure paraesthesia occurred in 75 per cent of the patients In about 200 cases pain radiating into the leg was caused by straining at stool, coughing, or sneezing The most constant objective finding was a positive straight leg reaction Other important manifestations consisted of localized muscle spasm and paraspinal tenderness, sensory changes in the fifth lumbar and first sacral dermatomes, and atrophy of the muscle groups in the gluteal region or in the calf An absent ankle jerk was noted in 43 per cent of the patients The cerebrospinal fluid contained excess of total protein in 53 per cent of cases, but evidence of fluid block was found in only 2 per cent of the series Routine radiography showed no finding characteristic of the lesion It is considered that surgical treatment should be employed in any patient who has been unable to work for several months owing to repeated disabling attacks of sciatica caused by a ruptured cartilage Operation is also required for the relief of root compression All the degenerated cartilage must be removed and, in some cases, the operation of fusion should be performed, especially in labourers

Diagnosis

Opaque myelography—Eaglesham refers to opaque myelography using Lipiodol (iodized oil) and Pantopaque for the demonstration of herniated discs in the lumbar region He recommends that the oil be introduced at a level above that of the suspected herniation through a sharp needle having a short bevel Three cubic centimetres of the oil will suffice although a larger quantity is preferable When the patient is lying prone the oil lies anteriorly where the deformity is greatest, the degree of lordosis or kyphosis having an influence on the depth or collection of the oil When the needle is left in position, care is needed in fluoroscopic examination Indentation at the level of the disc space or near it is usually found on the anterolateral surface of the oil column Displacement of the column is seen only in large herniations causing some degree of block With partial block an hour-glass appearance is seen With complete block, the oil column will be cut off abruptly in a transverse manner, simulating the presence of a tumour Lack of filling of the nerve root sheaths may be caused by disc herniation Errors in technique may have effects that are not easy to interpret A week should elapse between successive lumbar punctures

Pantopaque myelography—Echlin, Ivie and Fine emphasize the importance of pre-operative myelography lest the usual unilateral exploration for protruded intervertebral lumbar disc lead to the missing of bilateral or multiple protruded discs or other intradural pathological conditions Some surgeons have abandoned myelography on the grounds that clinical diagnosis is accurate and that the usual contrast media are unsatisfactory The authors report on 36 myelographies performed with the new contrast medium ethyl iodophenylundecylate, known in the United States of America as Pantopaque Pantopaque should be removed by aspiration through a 20 gauge needle immediately after the examination although, if left, it causes no greater reaction than does Lipiodol (iodized oil) and is largely absorbed A normal myelogram does not exclude herniated or concealed disc and the question of whether or not to operate may have to be decided on clinical findings Further, myelography should not be performed routinely or indiscriminately but only when careful history taking and neurological investigation suggest protruded intervertebral disc Only experienced persons should undertake the examination which should preferably be made in the presence of the surgeon who is to operate A Pantopaque shadow typical of herniated disc was demonstrated in 20 out of the 36 cases investigated and the presence of the lesion was verified at operation on 14 The remaining 6 were not operatively explored Myelography showed bilateral filling defects in 2 patients and evidence of diffuse intradural pathology, probably arachnoiditis, in 2 others Operation on one of the former revealed an unusually large protruded disc in the fourth interspace on the left and a large one in the fifth interspace on the right side, the nerve root in each case being markedly compressed, the symptoms had all suggested a left sided lesion only The other patient whose myelogram showed a bilateral filling defect also had symptoms referable to the left side only He was not operated upon as the condition had developed before he entered the Army

Characteristics of Pantopaque—Copleman maintains that the characteristic lateral defect in the opaque oil column which is indicative of a protruded intervertebral disc is absent in a small but significant group of cases in which the protrusion is small and central The patients in this group frequently complain of low back pain which does not radiate early in the course of the disease He describes the investigation of 5 such cases by the use of a new medium, Pantopaque This is a stable solution which is not miscible with spinal fluid Chemically it is a mixture of ethyl esters of isomeric iodophenylundecylic acids It is non-toxic and is not radioactive It is not opaque enough to obscure fine gradations of density No reactive arachnoiditis has so far resulted from its use The edge of the oil column should be allowed to advance slowly and gradually otherwise the bulk of the oil will obscure a small protrusion before its margins can be outlined Pantopaque maintains itself in a homogeneous column which fills the nerve sleeves very readily Copleman restates the difficulty which the great variety of conditions causing low back pain create in diagnosis Protrusion of an intervertebral disc when well developed may be detected in 60 per cent of cases by clinical methods, but the use of Pantopaque enables the investigation of the others to be carried out harmlessly and simply The diagnosis in the 5 cases described by him was confirmed subsequently at operation

Posterior herniation of lumbar discs.—The diagnosis of posterior herniation of the lumbar intervertebral discs is discussed by Munro, who states that there is great divergence of opinion concerning the criteria upon which such a diagnosis should be based. He analyses and compares the symptoms and signs of 2 parallel series of cases in both of which physical signs and history would generally be accepted as justifying the above diagnosis; in the first (78 cases) the herniation was proved and in the second (41 cases) another diagnosis was ultimately found to account for the syndrome. After a very careful analysis the author concludes that if a sensory loss corresponding to a lower lumbar or upper sacral root with atrophy and loss of ankle jerk is found, a diagnosis of irritation or compression of the root is justified. When there is a history of recurrent back pain radiating to the leg, especially to the lower leg, resulting from a back injury, often from a strain in lifting, and when the pain is made worse by coughing and sneezing, posterior herniation of a disc must be seriously considered as a cause of the root irritation. Spasticity of the lumbar muscles or alteration of the lumbar curve or the carrying out of Lasègue's test are in the author's opinion of no differential value. The level of the herniation cannot be determined on purely clinical grounds. Certain diagnosis depends upon myelography. Lipiodol (iodized oil) offers excellent contrasts but its use has certain objections and involves its subsequent removal. The use of oxygen or air presents considerable technical x-ray difficulty but the author has used principally air by the two-needle technique in this series. He and his co-workers report that a 20 per cent solution of Skiodan (Abrodil) satisfies all the necessary requirements of a contrast medium for the diagnosis of the condition. Munro concludes that clinical history and examination allows of the diagnosis of a suspected herniation but that contrast myelography either confirms or disproves it.

Herniation of nucleus pulposus

Cause of pain.—Larson presents the problem of the intervertebral disc syndrome and gives factual information and controversial opinion in regard to herniation of the disc. It is said that after the age of 25 years the discs are avascular and on that account are liable to pathological change. The question of the effect of injury in the form of strain or torsional stress in causing the syndrome is not settled. The cause of the pain is not clearly established; some patients have been relieved by operation; others have not. The pain may arise from pressure on the nerve roots or on the nerve fibres of the disc itself from degenerative changes or from other causes. Radiating pain is the outstanding symptom. It may be associated with paraesthesia or motor weakness in a small percentage of cases. Physical signs are equally difficult to explain. The onset of the pain, its distribution and type as well as physical signs of flexion or limitation and the condition of the reflexes require further corroboration by x-ray examination. Lipiodol or Pantopaque is injected into the spinal canal in order to determine the presence and the site of disc herniation. The results even then are not diagnostic because there is often discrepancy between operative findings and previous x-ray interpretations. Radiography for broken facets, fractures of bone, overgrowth of bone and neoplasm should be carried out. It is clear that a herniated disc cannot be recognized by a prescribed category of signs and symptoms. The diagnosis cannot rely on "classical history" since it is non-existent. When herniation of a disc is diagnosed and operative treatment is undertaken, the postoperative course alone can determine the effectiveness or otherwise of the treatment. When pain is intractable and resistant to conservative treatment, operative treatment may well be justified.

Conservative and operative methods.—Keegan discusses the diagnosis by neurological signs of herniation of lumbar intervertebral discs. In its early stages this condition is indistinguishable from other pathological conditions causing low back pain. Posterior displacement or partial herniation of the nucleus pulposus within the disc may often be reduced by manipulation. The patient complains of a very sudden, disabling low back pain which makes straightening of the back impossible and is often produced on very slight provocation. True herniation of the nucleus pulposus occurs through rupture of the enclosing annulus and the escape of an amount of fibrocartilage sufficient to produce an intraspinal tumour which presses on a nerve root. Pain in the hip or superior midgluteal region, radiating down the posterior thigh and calf and lateral ankle and foot, marks the area of distribution of the first sacral nerve root, the nerve most commonly compressed by herniation of the fifth lumbar disc. True sciatic neuritis would affect a much larger area of the leg, and the entire foot. Accurate nerve root identification can be determined by careful outlining of the nerve root areas of slightly reduced pain sensation—called dermatome hypalgesia—for each nerve root. Treatment should be conservative, by rest in bed, by traction, and by application of cast, brace or belt, since most patients recover without the need of surgical intervention. Recurring serious disability or continuing intolerable pain, however, indicates the presence of a fixed herniation requiring surgical removal. The operation is comparatively safe, does not cause damage to the back, immediately relieves pain and enables the patient to be on his feet in comfort within a short time. Motor regeneration may be expected unless an obstructive nerve root fibrosis has developed, but sensory regeneration may not occur. Trophic or sympathetic phenomena do not occur because of the absence of sympathetic fibres in nerve roots below the second lumbar root level.

In cervical region.—Michelsen and Mixter describe their findings in 8 cases of herniation of the nucleus pulposus of the cervical intervertebral discs. Pain and paraesthesias were common to all, as was a history of injury. In most cases the pain was more evident as a late than an

early symptom, and was exacerbated by certain movements of the neck and arms. In the 4 herniations occurring at the level of the fifth interspace, the sensory abnormalities involved the scapula, the anterolateral aspect of the upper arm, the antecubital space, the radial forearm and the thumb and index finger. Three of the herniations were at the sixth interspace and gave sensory signs over the scapula, the posterolateral aspect of the upper arm and the dorsal surfaces of forearm, and the index and middle fingers. In the remaining case the herniation was at the level of the seventh interspace, and the skin signs were over the scapula, the inner and upper arm, the forearm and the little finger. All these sensory signs followed fairly closely the patterns of the distributions of the sixth, seventh and eighth cervical nerve roots which are given on the standard dermatome charts. Motor dysfunctions included weakness, atrophy and twitchings of arm muscles varying with the site of the lesion. X-ray examination was greatly assisted by the use of Lipiodol. Narrowing of the sixth cervical interspace was seen in all the 3 cases at this level, and in 4 of the 8 cervical lordosis was seen to be absent. Laminectomy or subtotal hemilaminectomy gave good results—in some cases dramatic relief of pain, and in most, restoration of muscle function.

Instability of lumbosacral joint—The recognition of herniation of a nucleus pulposus as a cause of pain is quite recent. According to Smith, Deery and Hagman the relief from sciatic pain resulting from removal of the nucleus is so dramatic that persistence of pain in the lower back may be overlooked. The authors suggest that the cause of this back pain is a deranged or unstable lumbosacral joint and that it is possible that an unstable joint may be the underlying cause of weakening of the disc and overlying ligament, which in turn produces the herniation. The existence of an unstable joint can be shown by x-ray and suspected by the symptom of back pain, especially if it antedates the sciatic pain. The criteria for determination of an unstable lumbosacral joint roentgenographically are any one, or a combination of two or more, of the following: asymmetrical lateral articulations, anterior or posterior displacement of the fifth lumbar body, exaggeration of the lumbosacral angle, a thin intervertebral disc, and a transitional or partially sacralized lumbosacral vertebra. In a series of 100 cases of herniated nucleus pulposus an unstable lumbosacral joint was found to exist in 84. In 83 of these a spine fusion was performed in connexion with the removal of the nucleus. The Hibbs method was employed using a technique which permitted exposure of the disc laterally and excision of the herniation with the removal of very little bone. The time of operation was not greatly prolonged by the addition of fusion, which was done by an orthopaedic surgeon after a neurosurgeon had dealt with the herniation. Of 70 patients who were examined one year or more after operation, 24 were entirely free from pain, 33 had only slight pain and the remainder had pain sufficient to cause partial or complete disability.

Copleman, B. (1944) *Amer J Roentgenol*, 52, 245

Eaglesham, D. C. (1944) *Brit J Radiol*, 17, 343

Echlin, F. A., Ivie, J. McK., and Fine, A. (1945) *Surg. Gynec. Obstet*, 80, 257

Keegan, J. J. (1944) *J Amer med Ass*, 126, 868

Larson, C. B. (1945) *New Eng J Med*, 232, 137

Michelsen, J. J., and Mixer, W. J. (1944) *New Eng J Med*, 231, 279

Munro, D. (1945) *New Eng J Med*, 232, 149

Poppen, J. L. (1945) *New Eng J Med*, 232, 211

Smith, A. DeF., Deery, E. M., and Hagman, G. L. (1944) *J Bone Jt Surg*, 26, 821

SPLEEN DISEASES

See also B. E. M. P., Vol. XI, p. 401, and Cumulative Supplement, Key Nos. 1446–1452

Splenic diseases

Rupture of the spleen

Rare case of spontaneous rupture—Jones describes a case of spontaneous rupture of an apparently normal spleen. It occurred in a soldier aged 36 years, who had an attack of acute and sustained left abdominal pain. He vomited once at the commencement of the attack. He had never had indigestion, and bowels and micturition were normal. His general condition was good and pulse and temperature were normal. The abdomen was tender and rigid especially in the left upper quadrant. He was operated on as a case of perforated gastric ulcer, but the peritoneal cavity was found to be full of blood which was coming from the spleen, and a splenectomy was performed. Nothing else abnormal was found and he made a good recovery. The spleen was normal in size and was not abnormally mobile. There were several small haemorrhages in the pulp, one of which communicated with a large subcapsular haemorrhage. The arteries showed degenerative changes. The patient later gave a history of injury 3 months earlier to the right lower ribs. Previously reported cases have been attributed variously to a local splenic lesion causing the frequent dyspeptic symptoms, forgotten trauma, abnormal mobility of the spleen due to absence of the lieno-phrenic ligament and to early arterial degeneration of the spleen. Black states that at the age of 36 years, 50 per cent of spleens show hyaline vascular change. Jones suggests that the underlying cause of rupture is an intrasplenic haemorrhage for which no common cause is known. In the case cited there was no venous congestion, as has often been noted in other cases, but the blood vessels showed hyaline change.

Two cases of spontaneous rupture—McCarthy and Knoepf report 2 cases of spontaneous

rupture of the spleen. The first was that of a young male adult who complained of listlessness, epigastric pain and fever. Examination showed slight icterus of sclerae and mucous membranes, widespread lymphadenopathy, slight epigastric tenderness and a barely palpable spleen. Acute mononucleosis was diagnosed and was confirmed by a blood count. Seven days later the patient became acutely shocked with severe epigastric pain. Rupture of the spleen was diagnosed and splenectomy was performed. The spleen was enlarged, boggy and friable, with a ruptured subcapsular haematoma over the convex surface. The pathological report was of reticulo-endothelial hypoplasia with mobilization of fixed tissue elements. The patient made an uneventful recovery. The second case was that of a young adult male who complained of sudden acute epigastric pain, nausea, vomiting and diarrhoea. He gave no previous history of gastro-intestinal disease. The abdomen presented board-like rigidity. A raised leucocyte count suggested acute appendicitis. At operation, the appendix was found to be normal and there was free blood in the peritoneal cavity. Through a second incision, splenic rupture was found and splenectomy was performed. The patient made a successful recovery. The pathological report on the spleen was that there were multiple haemangiomas, with perforation of the capsule.

Jones, L. E. (1944) *Brit. med. J.*, 2, 561.

McCarthy, A. M., and Knoepp, L. F. (1944) *Amer. J. Surg. N.S.*, 65, 413.

STATISTICS, MEDICAL

See also B.E.M.P., Vol. XI, p. 438.

Interpretation of statistical data

Vital statistics for 1943 analysed

In the provisional analysis of the vital statistics for 1943 Stocks reports that during the first three quarters of the year the average death rate was 11.3, which is lower than that of the corresponding periods of 1938 and 1942. Owing to the influenza epidemic the rate rose to 14.6 during the last quarter of 1943, the deaths being most noticeable amongst the elderly. There was in consequence a slightly higher standardized death rate for the whole year than there was for 1942. There was little alteration in the total death rate from tuberculosis, but Stocks notes that whereas the death rates from respiratory tuberculosis showed increases in the age groups above 35 years in men, there was a decrease in the rates for women of all ages. Deaths from diphtheria declined between the ages of 1 year and 15 years but increased at other ages. The author suggests that had it not been for mass immunization 1943 might have shown a rise in the total deaths from diphtheria. Deaths from myocardial disease rose over the whole year, but analysis shows a decrease in the first three quarters and an increase in the last, which Stocks attributes to the effect of the influenza epidemic on the elderly.

Stocks, P. (1944) *Lancet*, 2, 65.

STERILITY

See also B.E.M.P., Vol. XI, p. 447; and Cumulative Supplement, Key Nos. 1455-1457.

General aspects

Causes of infertile marriage

Postcoital examination of cervical plug.—Barton and Wiesner discuss the Sims test, the name by which the authors suggest that the thorough investigation of sterility by postcoital examination of the cervix should be known. In this test the woman is examined 6-24 hours after intercourse during her period of ovulation, no bath or douching being allowed in the interim. Specimens of the vaginal pool and cervical or ovulatory plug are withdrawn by means of a bivalve speculum and a dry Green-Armytage syringe and are examined both when fresh and after they have been stained. The nature of the cervical plug is also noted. The test does not prevent fertilization and can be safely performed during pregnancy. During the presumptive ovulatory phase the cervical plug is normally clear and colourless and protrudes some distance from the external os; it should show dense invasion by sperm, 20 per cent of which, in most fecund couples, are still actively motile 24 hours after ejaculation. Staining will show various forms of cervical cells and spermatozoa, but the semen should always be stained separately for full cytological examination. It was found that the cervical plug may be mucopurulent or small, thick and difficult to withdraw, and yet may be capable of being invaded by sperm. The main importance of the Sims test in infecundity is to determine the density and depth of penetration into the ovulatory plug by motile sperm. It was found that a dense pool of healthy spermatozoa may fail to invade an apparently normal cervical plug, and therefore the capability of the sperm to invade the cervix cannot be determined by examination of the semen alone. Conversely a subnormal degree of invasion does not necessarily mean complete sterility, but only that fertilization is less likely to occur. The Sims test must therefore be used in order to supplement and not to replace other known tests for sterility, its use being chiefly to discover lack of cervical insemination after intercourse—one of the recognized causes of sterility not discoverable by means other than postcoital examination.

Sterility in the female

Treatment

Summary of essentials.—Schleyer discusses the prevention of sterility in women, the causes of which he enumerates as (1) hypoplasia of the uterus and the endocrine disorders, (2) malnutrition and lack of vitamins, (3) gonorrhoea, (4) chronic constipation, (5) abortion, (6)

toxic factors and (7) some contraceptives. The author emphasizes the great importance of early recognition of uterine hypoplasia and endocrine disturbance by mothers, teachers, welfare officers and others, who should immediately refer the patients for investigation and treatment. He considers that "any girls who have not established a regular, painless menstrual habit before the fifteenth birthday need to have their general health and endocrine status examined." He elaborates the nutritional factors involved with special reference to avitaminosis A, B and E and stresses the importance of adequate protein for children and young girls, whose needs in this respect exceed those of adults. Adequate variety, as well as quantity, of mineral salts is essential. Kennedy has shown that calcium deficiency causes sterility in animals. The author states that apparent cure of female gonorrhoea by administration of sulphonamides does not prevent Fallopian (uterine) tube blockage for which, in order to prevent sterility, he advocates repeated tubal insufflations as part of the after-treatment of gonorrhoea. In 1937 Schleyer specially investigated the relationship between inflammation of the rectum and sigmoid and sterility. He thinks that constipation may cause sterility in women in the following ways: (1) It may lead to pelvic cellulitis, uterine displacement, cervicitis and salpingitis. (2) It may cause congestion of the pelvic venous system with consequent oedema of the tubes and capsular thickening of the ovaries and interference with ovulation. (3) It may cause hormonal damage by resorption of toxins. (4) It may lead to ovarian prolapse with consequent interference with entry of ova into the tubes. The author advocates routine tubal insufflation after abortion in order to prevent secondary sterility. As toxic factors he mentions lead, tin, phosphorus, benzol, T N T, alcohol and tobacco. Contraceptives which destroy the normal vaginal hydrogen ion concentration or lead to cervicitis or endometritis, may cause sterility.

Sterility in the male

Conditions affecting fertility

Diagnosis and treatment—Walker discusses the diagnosis and treatment of male infertility. There are no reliable statistics but the author believes it to be probable that in about one-fifth the number of barren unions, the male is so infertile as to render pregnancy impossible and to make it improbable in two-thirds of the number. In the majority of cases, the condition can be detected only by means of semen examination, for outward signs are absent. The author considers that venereal disease, so stressed in the past as being a contributor to infertility, in fact rarely causes it. Since germinal cells are sensitive to pathological conditions, and especially to infections, in regions of the body other than the genital tract, investigation of sterility must include the whole body. Apart from a few cases of hypopituitarism, associated with hypogonadism, the author considers that endocrine disturbance is a rare cause of male infertility. Psychologically caused difficulties, notably ejaculatio praecox, often lead to sterility. Frequency of coitus is an important factor and, in the absence of other causes of sterility, weekly coitus is about twice as likely to lead to conception as is fortnightly coitus. Semen analysis is work to be undertaken by an expert. Condom specimens are deprecated because traces of chemical in the condom used may arrest the motility of the spermatozoa, a circumstance which has been known to lead to the making of an erroneous diagnosis of necrozoospermia which is a comparatively rare condition. Arrested motility may sometimes be due to warming of the specimen by the patient. The author considers that American authorities overrate the significance of the number of spermatozoa and says that it is nonsense to suggest that a man with under 60 million spermatozoa per cubic centimetre is to all intents and purposes sterile. It is quality not quantity that is of importance and a large percentage of abnormal forms is of unfavourable significance. Lack of cervical insemination is a frequent cause of sterility and the receptivity of the neck of the uterus is apparently at its height during the ovulatory phase. Testicular biopsy under Pentothal anaesthesia is helpful. The most effective testosterone preparation is a suspension of crystals of methyl testosterone. Surgical treatment is disappointing in its results.

Barton, Mary, and Wiesner, B. P. (1944) *Lancet*, 2, 563.

Schleyer, E. (1945) *Med. Pr.*, 213, 43.

Walker, K. M. (1945) *Proc. R. Soc. Med.*, 38, 243.

STOMACH, TUMOURS AND SOME OTHER CONDITIONS

See also B. E. M. P., Vol. XI, p. 476, and Cumulative Supplement, Key Nos. 1461-1464.

Malignant tumours of the stomach

Diagnosis and differential diagnosis

Relation of gastric carcinoma to gastric ulcer—Wiley discusses the relation of gastric ulcer and carcinoma in the light of recent literature and his own observations on a series of cases. He states that clinically the important point lies in the differentiation of the two conditions. He emphasizes that the initial symptoms of carcinoma of the stomach are minimal and the text book picture usually given is that of a late case. The average duration of symptoms in his series was 35 months for ulcer and almost 14 months for carcinoma. The author remarks that although there has been a great advance in the x-ray diagnosis of gastric carcinoma, most radiologists agree that it is impossible to differentiate the conditions in all cases and he states that most investigators with experience consider that a combination of radiology and gastroscopy offers the best chance of early diagnosis. Regarding the site of the lesion, Wiley thinks that all lesions of the prepyloric region and on the greater curvature should be resected owing

to the fact that such lesions often become malignant. Referring to the size of the lesion the author states that he has seen many large benign ulcers and he describes a case in which an enormous perforating ulcer was found to be benign. He emphasizes that it is often difficult at operation to decide whether the lesion is malignant or benign. He describes a case in which in spite of the prior radiological opinion and the opinion of the surgeon at operation subsequent section proved the lesion to be malignant. Wiley believes that the rate of healing of gastric lesions should be considered as a factor in diagnosis. If healing by medical treatment cannot be demonstrated by x-ray findings in about a month's time he advocates resection. He concludes that gastric ulcers, in contradistinction to duodenal ulcers which do not become malignant, should be considered as surgical problems in the first instance. He believes that increase of resectability rate by earlier diagnosis will offer the greatest hope in improving these patients' chances.

Treatment

Association of ulcer and carcinoma.—Sinclair, describing treatment of gastric neoplasms—which are, except in the rarest of cases, carcinomatous—emphasizes the need for careful and early diagnosis and stresses the fact that “simple chronic gastric ulcers which do not rapidly respond to adequate medical treatment should be under suspicion as carcinomas and operation advised”. He mentions that, although purely pathological evidence supports the accepted view that about 15 per cent of gastric carcinomata arise in pre-existing chronic simple ulcers, clinical evidence suggests a higher percentage. Site of growth may determine dominant symptoms. Pyloric growth manifests as pyloric obstruction whereas a growth situated high in the cardia suggests oesophageal obstruction; these localizing symptoms occur rarely and, unfortunately, late. The pyloric growth gives best results from radical surgery. There is an insidious type the chief symptoms of which do not focus attention on the stomach primarily. The history is rather of increasing lassitude and loss of interest in food than of dyspeptic trouble. In another type of case haematemesis is the chief symptom in a patient complaining of the abrupt onset of an indigestion the pain of which bears no particular relationship to eating. If a patient with known longstanding gastric ulcer amenable to medical treatment, loses the periodicity of attacks and a steady gnawing pain becomes noticeable which bears no relation to the taking of food, it is very probable that a carcinoma is developing. In addition to test meal, radiological investigation and general blood examination, gastroscopic investigation should never be omitted in all cases of indigestion which do not respond quickly to ordinary medical treatment.

Sinclair, N. (1945) *Med. Pr.*, **213**, 196.

Wiley, H. M. (1944) *Amer. J. Surg. N.S.*, **65**, 104.

STRABISMUS

See also B.E.M.P., Vol. XI, p. 492; and Cumulative Supplement, Key No. 1465.

Paralytic squint

Clinical picture

Eccentric fixation.—Guibor describes a case of eccentric fixation. The patient was a boy who had been under ophthalmic observation since the age of 8 months. At the age of 7 years when he was first seen by the author, unaided vision in the right eye was 20/20 : 14/14, and in the left eye, 20/50 (?). Corrected visual acuity in the right eye was 20/20 : 14/14, and in the left eye, 3/200 : 3/140. There was eccentric fixation in the left eye which converged and remained in a state of fixation in the eccentric position when the right eye was occluded. The author describes the disturbances associated with this eccentric fixation under three headings. (1) Disturbances associated with the motor apparatus. A left esotropia remained in the convergent position when the right eye was covered and even when glasses of, right eye, +7.00D sphere and left eye, +7.00D sphere, were worn. Thus the eyes continued to take up fixation with an area nasal to the true fovea. A slight weakness was present in the ability of the left external rectus to abduct the left eye and Guibor suggests that this may have been due to elongation of the left external rectus caused by lack of visiomotor impulses to this muscle. (2) Disturbances associated with the visual apparatus. In the visual apparatus the author found a severe amblyopia which did not improve when the fixating eye was occluded constantly for 4 months, a finding which suggested that there was some atrophy of the neurons in the visual pathway. There was a 5–7° absolute central scotoma with a normal peripheral field; normal projection was found but abnormal correspondence was present. (3) Disturbances associated with the proprioceptive apparatus. These may be said to have been demonstrated by rotation of the patient's head to the right, by his overshooting the mark in pointing and by his walking to the right of the line when the left eye was being used.

Treatment

Operation in adult cases.—The results of the operative treatment of 65 cases of strabismus in adults are reported on by Shure: the average age of the patients was 27 years. A complete investigation of the condition is of importance before treatment is attempted. The author describes the technique of operation. There were 51 cases of convergent, 12 of divergent and 2 of alternating strabismus. In discussing the operative results Shure concludes that recession of one muscle and resection and advancement of the opposing muscle is the surgical procedure which offers the best chance of relief for the patient. In the 55 cases in which this method was used, there was not any case of overcorrection; undercorrection occurred in

of agreement with the Wassermann reaction and Kahn tests, but which had the drawback that owing to the variable behaviour of the antigen used, a negative serum may seem to give a weakly positive finding. To a previously tested Kahn antigen the authors add certain exact quantities of colloidal benzoin, sodium chloride and sterile horse-serum, and titration against known positive and negative sera at different stages of the procedure give a more or less standard preparation. A large glass slide is marked off in 12 areas, and a drop of each serum, inactivated by heat, and a drop of the antigen are pipetted on to the appropriate space; both are then carefully mixed together with a glass rod. The slide is rocked gently a few times and is set aside for a time. It is rocked again just before it is read, which is done by viewing it against a black background in an oblique light. There is distinct precipitation and flocculation of the antigen in a strongly positive reaction, with complete or almost complete clearing of the turbidity. There is only partial clearing in a positive reaction and the flocculation is less distinct. There is no clearing and only fine flocculation in a weakly positive case. The mixture remains opalescent in a negative reaction and should not show any granulation. The length of time the tests should stand is most important, and is predetermined by testing the antigen with known strongly positive, positive, and negative sera. Two workers can do about 100 tests in 30 minutes. This method in comparison with the Wassermann reaction and Kahn tests gave considerably greater sensitivity, and continued to be positive later than either in cases of treated syphilis.

Indications for quantitative serological tests.—Heyman discusses the indications for quantitative serological tests and illustrates how these tests aid in the recognition of syphilitic infections. The method used to determine the quantitative titre of syphilitic serum is to dilute the serum until it ceases to give a positive reaction, the reagin titre being the greatest dilution that gives a positive result. A marked rise in titre easily identifies a lesion as primary syphilis when the dark-field examination is negative. A sharp rise in titre is usually found in recently acquired syphilis. A stationary titre indicates syphilis infection of some duration and a falling titre without treatment usually represents a false positive reaction. A reagin titre in the infant well above that of the mother is evidence of syphilis in the child. Quantitative tests should be made at regular intervals in order to determine in the child the disappearance of the maternal reagin and the gradual appearance of antibodies. This method of testing offers considerable aid in the recognition of relapsing cutaneous syphilis when all other signs are negative as a result of adequate syphilitic treatment. Some cases show a serological reversal for a time and subsequently without clinical symptoms a positive reaction develops. Quantitative tests show that these are cases of sero-resistance. The recognition of biological false positive reactions is often difficult but a rapidly falling titre in the absence of treatment is evidence of a non-syphilitic reagin. Children with a feverish illness may show a large titre of false positive reactions, those in adults being normally quite small.

Congenital syphilis

Diagnosis and differential diagnosis

Importance of rhagades.—Cerneva discusses the diagnostic value of the radial scarring of the lip in cases of congenital syphilis, and concludes that this sign is of great significance, although it is not very common and cannot be regarded as pathognomonic. The sign, which is of special importance in older children, in whom congenital syphilis may be less easy to diagnose than in infants, is, however, by no means always present in syphilitic children. In a recent survey of 273 such children rhagades were noted only 5 times; a series of 1,655 cases of proved syphilis included only 9 examples. On the other hand cracks at the corners of the lips are found in both children and adults who do not show any signs of syphilis. The cracks are characterized by a tendency to open in winter and to heal spontaneously in summer, and they eventually produce radiating scars indistinguishable from the rhagades of congenital syphilis. The cracks, despite the fact that no other evidence of syphilis is found, are best treated with a course of potassium iodide, under which they may be expected to heal in about a month. In newly-born infants the rhagades of congenital syphilis will heal completely without leaving the characteristic scars provided that specific treatment is begun early. Fissures at the angles of the mouth in young infants should always be looked upon as a very suspicious sign, calling for full investigation. The author, too, quotes a number of cases of adults in which the presence of radial scarring of the lips first suggested the diagnosis of syphilis.

Treatment

Arsenical compounds

Comparison of various methods in primary and secondary syphilis.—With the use of suitable but complicated adjustments for the purpose of correcting possible statistical errors, Usilton, Bruyere, Bruyere and Elliott analyse the results of 4,351 intensive treatments of patients displaying active evidence of primary or secondary syphilis. Results were more satisfactory in primary than in secondary cases and amongst the latter there were more serologically fast relapses after treatment with cases and serological and clinical relapses. Fewest relapses occurred after treatment with Mapharsen by rapid drip or with multiple injections of Mapharsen without vaccine or after most relapses were seen after multiple injections of Mapharsen without vaccine or after multiple injections of arsphenamine. Neoarsphenamine administered by slow intravenous drip gave best results in both primary and secondary syphilis but this form of treatment was abandoned because of the strong reactions it caused. The next most effective treatment was

multiple injection of Mapharsen with typhoid vaccine. Multiple injections of arsphenamine proved to be least effective, but analysis of the amount of arsenical administered by the various methods tried suggests that the poor results may have resulted from insufficient dosage. No significant differences were noted between the effects of treatment of infections and of reinfections, but primary cases, in first infections, gave better results than did relapses. Concurrent administration of bismuth appeared to reduce frequency of relapses in primary and secondary cases and to improve results in treatment of secondary cases. Race, sex and age all influenced the effects of intensive therapy, non white females under 25 years of age proving to be most resistant to treatment. Patients aged over 25 years responded better than did those under that age, males responded better than did females, and whites than non whites. Patients with a Kahn test reaction of 20 or under responded better to treatment and relapsed less frequently than did those who showed a titre of 20 or over. Encephalopathy occurred more than twice as often amongst whites as among non whites and appeared to be more often fatal in white females than in white males or in non whites of either sex, but its incidence was apparently uninfluenced by type of treatment.

Prevention of postarsenical jaundice—Salaman, King, Williams and Nicol consider the prevention of jaundice arising from antisyphilitic treatment in the light of recent evidence that this condition is due to the transmission of an infective agent through the medium of syringes contaminated by blood. The usual clinic technique which involves the sterilization of needles but not of syringes is described and it is pointed out that the increased number of patients, the shortage of syringes and the known higher incidence of infective hepatitis among the general population have rendered this technique more dangerous than formerly it was. The new technique devised by the authors involves the use of a sterilized syringe and needle for each patient. The medical officer should wash his hands between injections. All new syphilis patients were treated by this method and old cases diagnosed and treated in part at least by the authors formed the control group. Comparison between the experimental and control groups was made at 120 days and at 180 days. Intravenous Mapharside and intramuscular bismuth were used throughout. In the experimental group only one case of jaundice developed among the 36 treated for more than 4 months and of these 18 received treatment for at least 6 months. In the control group of 67 cases there was a jaundice incidence of 37 per cent within 4 months and 68 per cent of 56 men were affected within 6 months. The highest incidence was between the third and the fourth month but in some 20 per cent the disease developed later than the sixth month. The authors believe that postarsenical jaundice can be transferred by improperly cleansed syringes and that it can be prevented by improved technique. They do not imply that injection thus transferred is the only cause of the condition and the occurrence of true hypersensitiveness to arsenic, as in Milian's syndrome is stressed.

Side effects of arsphenamine treatment—their prevention and treatment

Occurrence of acute yellow atrophy—A rare case of acute yellow atrophy occurring in early syphilis is described by Leonard. The patient was a girl, 15 years of age, in whom a rash and jaundice developed 3 weeks after the appearance of a primary labial sore. There was pyrexia, marked jaundice, a widespread papular eruption and a purulent vaginal discharge. The liver and spleen were not palpable. Wassermann and Kahn reactions were strongly positive. The van den Bergh reaction was positive immediate direct. The icterus index was 45 and the prothrombin time less than 20 per cent of the normal. An x ray film showed a liver apparently normal in size. Specific therapy with Mapharsen and bismuth was started. A typical reaction occurred after the first injection and a milder one after the second. The skin lesions began to clear but the jaundice did not improve and 3 days after the last Mapharsen injection the general condition deteriorated with the onset of stupor, hyperactive reflexes, positive Babinski reflex and dilated pupils. The patient died. Post mortem examination showed typical acute yellow atrophy and cerebral oedema. The question arose whether the patient had acute yellow atrophy from the start or whether she had syphilitic hepatitis which developed into acute yellow atrophy on account of the hepatotoxic effect of Mapharsen of which only 3 doses of therapeutic size had been given. In the 31 recorded cases of syphilitic hepatitis with jaundice, arsenic therapy cleared the jaundice rapidly and in none did acute yellow atrophy develop. Improvement in cases of syphilitic hepatitis treated with the heavy metals was much slower. The published weight of evidence is in favour of the use of arsenic in the jaundice of early syphilis. It remains to be shown which causes the more permanent liver damage—the rapidly acting more toxic arsphenamine or the longer course of syphilitic hepatitis that occurs during treatment with the heavy metals.

Use of sulphur containing amino acids—Beattie and Marshall report on the use of sulphur-containing amino acids in the prevention of postarsphenamine jaundice. The work was based on the observations of Miller and Whipple, who found that the administration of methionine to protein-depleted dogs averted the onset of liver damage after chloroform anaesthesia. Prior to the experiments the greatest incidence of jaundice had been noted between the fourteenth and nineteenth week of antisyphilitic treatment. Accordingly, alternate patients arriving at the fourteenth week of treatment were chosen as controls and were not given any amino-acids. One group received a dried casein digest preparations of sulphur-containing tryptsin digest of pure casein. The powder was unpalatable, but a maximum amount of 10 grammes a day was given in capsules. In another series of cases cystine was added so as to

provide a methionine content of 467 milligrams per diem. Other patients received either cystine alone or pure methionine. It was found that no preparation was effective in reducing the incidence of liver damage. Some preparations, however, had the effect of moderating the severity of liver damage and delaying its onset. It was concluded that cystine diminishes the toxic effects of the trivalent organic arsenicals by virtue of its reduction to cysteine in the liver. In fact, large quantities of cystine may impede the action of antisyphilitic treatment. Moreover, the effect of cystine on established liver damage may be conducive to cirrhosis. Methionine remedies a specific dietary deficiency and 2.5-3 grammes should be given daily. This quantity may be supplied either in the form of the synthetic compound or by the addition to the diet of 1 pint of milk. Synthetic methionine is more effective than is an equivalent amount of casein digest reinforced with cystine.

Combinations of bismuth and arsenic

In early cases.—Eagle reports the results in 4,823 patients of treatment of early syphilis with injections of Mapharsen given three times a week. Each dose was approximately 1 milligram per kilogram of body weight with a maximum of 80 and a minimum of 40 milligrams. When continued for 9-12 weeks and used in combination with weekly injections of 0.2 gramme of bismuth subsalicylate, a state of cure was estimated to occur in 85-90 per cent of cases. Without bismuth, Mapharsen alone gave uniformly poor therapeutic results. Within fairly wide limits the total duration of treatment had no effect on the end results provided that the patient eventually received the scheduled total amount of the drug, namely 1,600 milligrams. The initial reagin titre affected the rate at which seronegativity was obtained but did not affect the ultimate percentage of patients considered to be cured. Treatment had to be interrupted because of toxic reactions in 106 patients; 39 of these were severe reactions with jaundice the most common complication. Four deaths occurred, 2 from nephritis, 1 from jaundice and 1 from toxic encephalopathy, all between the second and the fourth week of treatment, a period in which the majority of toxic reactions were noted. The incidence of toxic reactions was highest in young negro women and there were no deaths among the 2,583 men. Eagle states that Mapharsen and bismuth are apparently not merely additive but actually synergistic in their therapeutic effects. This suggests that they may exert spirochaeticidal action by affecting different vital functions of the organism. It is, however, conceivable that bismuth postpones infective or serological relapse, a possibility which several years of observation will be required to substantiate. Although previous studies have suggested that the prognosis of early syphilis is better in secondary syphilis than in the seropositive primary stage, Eagle's analysis does not lead to that conclusion.

Pyretotherapy

Combined with chemotherapy, in early syphilis.—Kendell, Rose, Miller and Simpson review their experience since 1932 with the use of combined artificial fever and chemotherapy in early syphilis. Their observation that clinical relapse will usually be anticipated by changes in the serological course, as measured by the quantitative Kahn titre, provided an important prognostic guide in assessing therapeutic results. The authors refer to their earlier experience and to their consideration of the experimental finding that a subcurative dose of neoarsphenamine, given immediately prior to a subcurative session of artificially induced fever, gave better results in treating syphilitic rabbits than the administration of greater amounts of the drug or of fever alone. They were encouraged to undertake an investigation into the possibility of curing human syphilis by combining large doses of Mapharsen and bismuth with one session of fever, and they selected 31 patients with primary lesions and 6 with secondary syphilis for intensive treatment. An intramuscular injection of 4 grains of bismuth subsalicylate (bismuth salicylate) was given immediately before commencing a 10-hour session of fever at 106° F. (rectal), during which period between 120 and 240 milligrams of Mapharsen was injected. The lesions healed in 1-2 weeks. Kahn quantitative serological examinations were done weekly until negativity was attained, subsequently at progressively longer intervals. The progressive decline in titre to negativity was essentially the same as that noted for patients receiving a larger total amount of both artificial fever and chemotherapy over a longer period. In early syphilis the lower the pre-treatment titre the more rapid the serological reversal to negativity. At present, the authors do not recommend this intensive course of reversal to negativity. They noted unduly frequent evidence of hepatic and renal changes, attributable to arsenic and bismuth. The brain of a patient, who died 3 days after treatment, contained arsenic, particularly in the medulla.

Early acquired syphilis

A 5-day course of intravenous arsenic.—Recently the treatment of syphilis with arsenical preparations has tended to become more intensive. Francis and Wannan give details of a 5-day course of intravenous massive-dose arsenical therapy with observations on serological reactions. The patients were selected as having early syphilis and as being suited mentally and physically for the form of treatment. Each patient was tested for idiosyncrasy by administration of 0.04 gramme of Mapharsen 3 days before intensive treatment was started. A daily dose of 0.24 gramme of Mapharsen dissolved in 2,000 cubic centimetres of 5 per cent dextrose in double distilled water was administered intravenously at the rate of 200 cubic centimetres per hour for 10 hours; a fresh solution was made as required every 2½ hours, and thus many of the toxic symptoms of the drug were avoided. The total dosage for the 5 days was 1.2

grammes. By this method 22 patients were treated and serological tests were made each week for 10 weeks and afterwards once in every 3 months. Of 7 patients with primary syphilis, whose blood before treatment failed to react to serological tests, 5 continued not to react, and in 2 a slight titre developed, one disappearing after one week and the other after two weeks. Thirteen patients had primary syphilis showing a +4 reaction before treatment. The serum of 3 ceased to react 1 week after treatment, 1 after 2 weeks, 2 after 3 weeks, 1 after 4 weeks, 3 after 5 weeks, 1 after 7 weeks and 2 after 8 weeks. Two cases were considered as being failures. The clinical signs disappeared but serologically there was no difference in titre 10 weeks after the end of treatment. One patient, treated with 0.04 gramme of Mapharsen given by injection 4 times a day over a period of 5 days, ceased to react to serological tests in the fifth week and has so remained for 11 months. There was one complication only among some 40 patients treated, 1 patient dying from encephalitis haemorrhagica soon after the completion of the course.

Penicillin

Serological records—Mahoney and others record their findings of the post-treatment observation after 300 days of 4 patients previously reported on as having been treated with penicillin for early syphilis, and interesting items of information from a further study of 100 cases are given. All of the original 4 patients obtained rapid healing of the penile ulceration. Three of them reached seronegativity within 3 months and maintain it still. In the fourth case there was a negative serological test on the seventy-first day, negativity continuing until the two hundred and eighty-sixth day, when strongly positive reactions were recorded. This case is regarded as having been reinfected. In the study of the additional 100 cases, 1,200,000 units of penicillin were injected intramuscularly in 20,000 unit doses at 3-hourly intervals for 60 injections. All but 3 were cases of primary or secondary syphilis. Since the lesions tend to disappear rapidly, success or failure is interpreted by the serological reactions. The records are examined of those who had 75 days of satisfactory subsequent observation, 52 cases fell in this group, and the average duration of observation was 135 days. Of these, 31 are considered to have responded favourably and 7 show a steady decline in the serological titre and are regarded as probably favourable. In 7 who had shown a trend towards seronegativity for a time, higher titre reactions subsequently developed. The remaining 7 display serological reactions which are difficult to classify as tending to be favourable or unfavourable—they are probably unfavourable. Of these 52 patients, 30 had primary syphilis. Two of them had clinical relapse and one had a serological relapse after 112 days. Two others with a protracted trend towards reversal are not classified. The remaining 25 are clinically and serologically negative. Of 22 secondary syphilitics, 11 have attained or have nearly attained seronegativity, 4 show a tendency to recurrence of higher titre reaction, and 7 are regarded as failures. Patients with early syphilis respond in a satisfactory manner, those with secondary syphilis require more intensive therapy.

General

Review of present-day methods of treatment—Mascall reviews the different forms of the modern treatment of syphilis, pointing out their relative merits and defects. Diagnosis of syphilis cannot be made in the absence either of the *Treponema pallidum* in the lesion or of a positive serological reaction carried out by a competent pathologist. The objects of treatment are to prevent transmission of the disease and to cure the patient. Treatment should be started as soon as the diagnosis is confirmed. Indications of intolerance to the drugs employed must be sought and treatment must be controlled by periodic clinical and serological examinations. The arsenical preparation most commonly employed is neoarsphenamine, given intravenously, the dose being dissolved in 10 cubic centimetres of sterile water. Tryparsamide and Acetylarsan are most often used for tertiary syphilis, and an oral preparation, Stovarsol (acetarsol), is used in the treatment of congenital syphilis. Mapharsen and Neohalarsine (arsphenoxide tartrate), since they are rapidly excreted from the body, are used in the intensive treatment of syphilis. The bismuth preparations most commonly employed are metallic suspensions in water or glucose and insoluble compounds suspended in water or glucose. Two main schemes for treatment are recognized, the intermittent concurrent and the continuous alternating. In the former, 10 injections of neoarsphenamine and 10 injections of bismuth constitute a course. A rest of 3 weeks intervenes before the next course is given, the number of courses depending upon the stage of infection at the beginning. Two full courses are given after the Wassermann reaction has been negative. In the continuous alternating scheme no rest intervals occur, the administration of neoarsphenamine alternating with that of the bismuth preparation. In the intensive treatment Mapharsen may be given by the continuous drip method, slow or rapid. Usually, however, 60–100 milligrams are injected by means of a syringe, once or twice daily, until 1,200 milligrams have been administered. It is believed that a induced fever therapy decreases the toxic effects of arsenic. Treatment by penicillin (40,000 Oxford units) injections, repeated every 3 hours for 7½ days, is highly satisfactory although relapses are known to occur. In tabes dorsalis and general paralysis of the insane, tryparsamide is given in 10 injections and 10 injections of bismuth are given afterwards.

Review of methods in use

Budd and Budd review progress in the treatment of early syphilis. Until 1932 the current systems were continuous alternating or alternating intermittent therapy using arsenic, bismuth and sometimes mercury rubbings. Since the introduction of massive intravenous therapy many

related methods have been introduced and the authors briefly summarize them. Chargin, Leifer and Hyman in their original report on massive arsenotherapy reported on 25 patients, 15 of whom were under surveillance for a long time; 13 were clinically and serologically well after 5 years. In their second series of 86 cases there was a fatal case of haemorrhagic encephalitis. Subsequently, using Mapharsen in a very large number of cases until 1940 these workers had not had a fatality. Thomas and Wexler were of the opinion that Mapharsen in doses totalling 1 gramme given by the multiple syringe method, and with hyperpyrexia, compared equally with the intravenous method of massive arsenotherapy. Eagle reported on the method of tri-weekly doses of Mapharsen. With a total amount of 1 gramme or over combined with weekly doses of 0.2 gramme of bismuth salicylate, upwards of 82 per cent of cures were obtained. Shock and Alexander reported on a small series of patients treated with daily doses of Mapharsen for 12 consecutive days, but Budd and Budd remark that a larger series will be necessary before there can be a final evaluation of the method. Moore and his colleagues in a preliminary report on 1,418 cases of early syphilis treated with penicillin concluded conditionally that it appeared to be 90-95 per cent effective and compared favourably with massive arsenotherapy. Concluding that all present-day methods are of comparable value it remains to be decided which method is the most practical for any individual patient. Rattner has suggested for public clinics, the multiple syringe method, for private practice, the tri-weekly regimen, and when the time factor is of imperative importance, the 5-day intravenous therapy.

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TESTIS AND CORD DISEASES

See also B.E.M.P., Vol. XI, p. 656.

Tumours

Morbid anatomy

Carcinoma testis and oestrogenic activity.—The similarity of the signs and symptoms of carcinoma of the canine testis to the changes caused in male dogs by the experimental administration of oestrogens is described and discussed by Mulligan. Six cases of carcinoma of the testis in dogs, taken from the literature, showed a definite syndrome. The dogs were of various ages from 2 to 12 years, and of various breeds: Pomeranian, Boston terrier, wire-haired fox-terrier and fox-terrier, and the growths were 3 in cryptorchid and 3 in scrotal testes. Adenocarcinoma was the neoplasm found, with varying degrees of atrophy of the seminiferous epithelium of the opposite testis. Stratified squamous epithelial metaplasia of the prostatic urethra, ducts and acini, with hypertrophy of the prostate, was found, as well as hyperplasia of the ducts and acini of the breasts, with mammary enlargements, swelling of the penile sheath, loss of hair, attraction of other male dogs and depression of libido. Observations were also found in the literature on the effects of oestrogens in male dogs; these were aspermatogenesis, and varying degrees of atrophy of the germinal epithelium of the testes, with fibrosis of the stroma and the other signs and symptoms mentioned above. In recent experiments 4 dogs, weighing from 15 to 27 pounds, were given 330-2,985 milligrams of stilboestrol in periods of 192-291 days, as well as, in 3 cases, the implantation of 500 milligrams of stilboestrol in the right upper quadrant of the ventral abdominal wall. The syndrome developed in all the animals. Three of the dogs were sacrificed for pathological investigation, and as well as the mentioned pathological changes in the sex organs, degenerative changes in the skin and the thyroid and suprarenal glands were noted. The dog left alive had completely recovered from the signs of feminization about a year after administration of stilboestrol had been stopped. The similarity of the changes noted suggest that carcinoma of the testis elaborates oestrogenic material or at least a substance metabolically altered to a compound having a feminizing action.

Clinical picture and course

Review of sixty-two cases.—Vermooten presents an analysis of 62 testicular tumours seen in 2 years at an army hospital in the United States of America. Early diagnosis was favoured by regular medical inspection and by the routine of army life. Regular shower baths, long tramps,

callisthenics and combat training all tended to draw the patients' attention to the lesion, which may explain why the incidence in the army is greater than it is in the civil population. Trauma bore no aetiological relationship to the lesion except that it aided discovery. When they were first seen most of the tumours were mistaken for epididymitis, orchitis or hydrocele. Eleven tumours were benign and 51 were malignant. Vermooten emphasizes the difficulty of differentiating by clinical tests alone between a benign and a malignant growth and he states that if it is necessary to open the tunica albuginea for diagnostic purposes the surgeon should do an orchidectomy even though he removes a benign tumour. Testicular tumours when malignant spread too rapidly to risk disseminating them. In radical orchidectomy ligation of the cord high up is essential in order to avoid early extension along the lymphatic vessels, so as to reduce the possibility of local recurrence and to ensure that should there be recurrence at the site of the cord division, the tumour will grow intra abdominally. This is not so distressing as a fungating mass in the wound. Whether there is clinical evidence of metastases or not, the orchidectomy should be followed by high voltage x ray therapy to the abdominal lymphatic glands on both sides in the region of the renal vessels. Of 51 patients with malignancy, 11 died, 6 are alive with metastases and 36 are alive without clinical evidence of metastases. Sixteen of these have survived for periods of between 1 and 2 years.

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TESTIS, UNDESCENDED

See also B E M P, Vol XI, p 671

Treatment

Surgical

The modified Torek operation—Iason discusses cryptorchidism, of which there are 2 types—the incompletely descended testis arrested at a stage of its normal descent, and the ectopic testis. The undescended testis is normal in structure but is not fully developed and may be caused by hypopituitarism, primary hypogonadism or hypothyroidism. Ectopia testis is due only to mechanical factors and does not respond to hormone treatment, the testis may be pubopeneile, femoral or perineal in position or in the superficial inguinal region. It is normal in size and is usually accompanied by an indirect inguinal hernia. After puberty the ectopic testis may fail to generate a mature germinal epithelium on account of the abnormal temperature outside the scrotum, the retained testis even in adults may regenerate if it is placed in the scrotal sac. Substances used for treatment of retained testis are the anterior pituitary-like substance which occurs in the urine during pregnancy, anterior pituitary extracts, pregnant mare's serum and testosterone propionate. The results depend partly upon anatomical factors which cause immobility of the testis. Surgical treatment is contra-indicated in retained testis except when used in conjunction with endocrine therapy. It is the method of choice in ectopia testis. A testis placed in the scrotal sac before puberty, produces hormone and sperm, the undescended testis is more liable to malignant change, trauma, torsion, inflammation and strangulation. Surgical treatment is preferably, but not exclusively, carried out before puberty, a modified two stage Torek operation being performed. The testis is exposed and freed through the usual inguinal scrotal incision. The base of the scrotum and the contiguous surface of the corresponding thigh are incised and the posterior margins of the incisions are sutured. The testis is drawn down to the scrotal wound by traction on the gubernaculum, which is then transfixed to the deep fascia of the thigh. The anterior margins of scrotal and thigh wounds are sutured.

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TETANUS

See also B E M P, Vol XII, p 1, and Cumulative Supplement, Key No 1481

Clinical picture

Clinical types

Report on two cases, one local—Cole gives details of 2 cases, one showing severe local tetanus in a mild generalized attack, the other being a typical example of severe tetanus. (1) A boy aged 5½ years had trod with his left foot on a rusty nail. Three days afterwards he felt ill, complaining of abdominal pains and difficulty in opening the mouth. He was then admitted to hospital showing characteristic signs of tetanus. The foot and the leg on the left side were slightly stiffer than those on the right. The patient received 200,000 units of antitoxin, chiefly intravenously. As the general signs developed, rigidity of the left leg became more marked until it was in continuous muscular spasm, in striking contrast to the other limbs. Administration of bromide, 10 grains every 4 hours, and of paraldehyde, 1½ drachm per rectum at night, induced sleep. The rigidity of the left leg persisted throughout the illness and was the last sign to disappear. (2) A boy, 8 years of age, sustained an abrasion on the dorsum of the right foot and 10 days afterwards was admitted to hospital with pronounced signs of generalized tetanus. Antitoxin, 100,000 units, was given intravenously, the boy's condition being critical. For the purpose of controlling the spasms and of promoting sleep paraldehyde in doses of 3 cubic centimetres was given intramuscularly twice every 24 hours, and proved to be effective. In order to counter dehydration an intravenous drip was set up,

the needle being kept in the vein by a plaster of Paris splint applied to the forearm. As pneumonia appeared to threaten, sulphathiazole was given. The boy made a gradual recovery. Cole, L. (1945) *Brit. med. J.*, 1, 219.

THERAPEUTICS GENERAL

Modern therapeutics

Evolutionary history

In a presidential address to the Cambridge Medical Society, Langdon-Brown deals with the evolution of modern therapeutics from the times of Aesculapius and Hippocrates, the Aesculapian cult employing psychotherapy and suggestion, and the Hippocratic, observational methods, relying on the doctrine of the four humours. After Galen medical science was lost until the Renaissance. At the beginning of the 19th century treatment was largely eliminative, by purgatives, emetics, diaphoretics, diuretics and bleeding. Later came new methods of diagnosis—auscultation and percussion—and physical signs found during life were compared with lesions found after death. The first synthetic preparation to be used clinically, antipyrin, a phenol derivative, contained a benzene ring, but the discovery of the importance of benzene rings in metabolism was made much later. Endocrinology and immunology came to the fore and then, in the 20th century, the recognition of deficiency diseases and the necessity for exogenous as well as endogenous catalysts in the biochemistry of the body. A new conception of the action of drugs was caused by the discovery that every nervous stimulus to the tissues is mediated by a chemical action, and that sympathetic nerve endings liberated adrenaline or acetylcholine. Ephedrine and Benzedrine (amphetamine), Eumydrin (atropine methylnitrate) and Prostigmin are examples of drugs which affect sympathetic action in one way or another, and help or bar the entrance of stimuli into the cell. The last great advance is chemotherapy, with the sulphonamides and other bacteriostatic drugs, and penicillin. It has lately been realized that the hypophysis is a great transformer of nervous activity into chemical activity which stimulates or inhibits other ductless glands by the appropriate trophic hormone. The hypothalamus in its turn receives impulses from the cortex, and therefore the psychic state can play on the endocrines through the hypophysis just as the endocrines can modify the psychic state. Insulin, metrazol (leptazol) and electric shock treatment and later prefrontal leucotomy, are developments in the physical treatment of mental illness; on the other hand psychic causes for somatic disease are recognized, the latest development in modern therapeutics being recognition of the psychosomatic factors in disease—in a way a return to the Aesculapian cult. We have, however, now a much clearer view of fundamental principles of therapeutics.

Drug administration

The main principles

Hunter maintains that the patient's demand for a bottle of medicine does not extend to watery-looking tasteless mixtures. Liquids are preferred to pills or powders, and injections are considered to be of great potency. A placebo aids recovery by increasing the patient's confidence. Moreover, if the diagnosis is obscure, the medicine may encourage the patient to attend for further observation. A useful prescription combines the sedative effect of sodium bromide with the tonic action of nuxvomica. It is a mistake to give large quantities of medicine for an acute illness or a small supply of medicine for chronic conditions. Drops for the eyes and ears should be ordered in moderate amounts, namely, 120 minims and half a fluid ounce respectively. One ounce of ointment is sufficient except for the treatment of scabies, which in the case of an adult requires a pound of sulphur ointment. Samples of new untried compounds should not be distributed indiscriminately because further supplies, even if they are obtainable, may be too expensive for the patient to buy. The cost of a drug is an important factor, especially in the case of proprietary preparations. It is better to rely on a few old remedies with simple formulae. Accurate dosage is ensured by the use of a graduated medicine-glass rather than spoons of varying capacity. A patient with an idiosyncrasy to a drug should be warned to draw attention to this fact at any future consultation. Patients treated with digitalis, sulphapyridine and other potent drugs require supervision for evidence of overdosage, but minor reactions should not be allowed to imperil completion of treatment. The drugs of addiction include alcohol, morphine, diamorphine and cocaine. Recurrent symptoms should not be treated with these drugs unless the disease is painful and incurable, as in the case of inoperable carcinoma.

Chemotherapy

Inhalation methods

Mutch describes the result of an enquiry into the possibility of administering chemotherapeutic substances by the lungs in clinically significant amounts, either for action on the lungs themselves, or for general therapeutic purposes. Sulphonamides, on account of their low toxicity and relative non-irritant action on the pulmonary mucosa, were chosen as test substances, and the solutions used were a 50 per cent weight in volume aqueous solution of stances, and the solutions used were a 50 per cent weight in volume aqueous solution of sulphonamide E.O.S. (the *p*-ethyl- α -sulphonate of aminobenzene sulphonamide), the mist of which can be inhaled without causing the slightest discomfort, and 30 per cent soluble sulphacetamide, which is also non-irritant to the lungs, although it causes some eye irritation

which passes off in a few minutes. Mists were produced by the Collison inhalation apparatus, which gave the best results when its standard oro-nasal face-piece was replaced by the rubber valveless nose piece of the standard B L B Mask, expiration taking place through the patient's mouth. In order to test absorption, experiments were made on 13 volunteers—10 normal young men and 3 patients with bronchiectasis. The amount of the drug absorbed was calculated from the amount found subsequently in the urine and in the blood, the bronchiectatic patients absorbing more than the normal students. With a 50 per cent weight in volume aqueous solution of sulphonamide E O S, nebulized by 6-8 litres of oxygen per minute, the patient absorbs about 1 cubic centimetre of the original solution, or 0.5 gramme per hour. Mists may be used for respiratory conditions in which the air passages are unobstructed, such as asthma, bronchitis, irritant gas-poisoning, bronchiectasis or lung cavitation, and for the administration of drugs which are destroyed when given by the mouth, such as penicillin, organic arsenicals, insulin, parathyroid extracts and extracts of the posterior lobe of the hypophysis. In the case of penicillin, a total of 1 hour's inhalation per day of a 25 per cent solution (400 units per milligram), nebulized in a Collison apparatus and administered through a valveless closely fitting nose-piece, would deposit 100,000 units in the respiratory tract.

Electrical shock therapy

Review of results

Katznelbogen, Baur and Coyne describe some clinical, biochemical and morphological results of electrical shock treatment of 276 patients. It was found that a patient's tolerance of the electric current may change at intervals of minutes or days. The tolerance may remain great or may diminish considerably within a few minutes. The latent period was usually 3-5 seconds, occasionally 20-30 seconds. *Petit mal* reactions occurred with currents of from 350 to 675 milliamperes for $\frac{1}{16}$ second, but considerably fewer at the higher load. Severe and moderate convulsions were produced by currents of from 300 to 600 milliamperes, the higher currents producing severe convulsions much more frequently. Some unusual reactions occurred, including two convulsions from one application, and convulsions of long duration or of unusual type. In one case a convulsion lasting for 50 seconds resulted in apnoea for 6 minutes which yielded to treatment. Complaints of nausea, headache and fear of the treatment were made by a few patients. Nine fractures occurred, 3 of the head of the humerus, 5 spinal and 1 of the femur. Of the psychotics treated many recovered or showed improvement although there were a number of relapses among the schizophrenics. Out of 9 psychoneurotics there was no recovery, and only 5 showed improvement. Specimens of urine obtained before and after treatment showed little significant change except in specific gravity. Changes occurred in the cellular and chemical constituents of the blood as well as in the icteric index, increases were more often seen than were decreases except in the case of the amino acids and carbon dioxide, the last named of which was decreased after nearly all treatments.

Insulin shock therapy

In cases of neurosis

Sands describes a modified insulin shock treatment for certain forms of neurosis, which is without the potential dangers of other physical methods. Out of 850 cases so treated at Sutton Emergency Hospital, England, 320 have been selected as specially suitable. The object is to produce not coma but a mild hypoglycaemic state, with perspiration, flushing of the skin and drowsiness from which the patient can be easily roused. The amount of insulin required varies from 10 to 100 units, and treatment is given on 6 days a week for 2-5 weeks, until gain in weight stops. The treatment has been found to be of great use in acute anxiety states, in hysteria and in mixed conditions of anxiety and hysteria, with loss of weight, as well as in neurasthenic states of exhaustion and irritable weakness. In depression the fundamental mood disorder is not affected by insulin, but the physical state of debilitated patients is improved, and insulin is useful in cases in which the depression is subacute and mainly exogenous. Patients are rendered more responsive to psychological treatment and a combined insulin and continuous sleep treatment has been found by Sands to be very effective in cases in which there is great tension and malnutrition. The mode of action is mainly metabolic, insulin causing increased metabolism and raised respiratory quotient, with marked stimulation of appetite and increase of weight up to 1 pound or more daily. The growing sense of wellbeing produced has necessarily a suggestive psychological effect. The results of the treatment showed improvement in all but 6 per cent of cases and patients were able to be discharged within 3 or 4 weeks.

Proctology

Main principles of rectal surgery

Reviewing present-day proctology, Terrell stresses the objective of rectal surgery, namely the removal of the pathological condition without impairment of function. There is rarely any good reason for loss of control to occur. In the past, the most common cause for it was the forcible dilation of the sphincter muscles as a preliminary step to operation but this procedure, like the use of the rectal plug, has been abandoned. In fistula it is best to leave the tract open to heal by granulation without packing the wound. A perirectal abscess is the first stage of a fistula and removal of the latter is usually necessary for cure. Spasm of

the coccygeus, piriformis or levator ani may cause symptoms of pressure and aching in the rectum which can be relieved by regular massage of these muscles. Only simple uncomplicated internal haemorrhoids are suitable for treatment by the electric needle or by injection. Surgery is indicated in all cases of haemorrhoids associated with other diseases such as cryptitis, papillitis or fistula. Good postoperative treatment in rectal surgery allows soft diet the morning after operation and bowel movement in 48 hours, the patient being allowed up and on full diet thereafter. In Terrell's opinion local application of sulphonamides to wounds does not reduce the time of healing. Opium is not a local anaesthetic, and when it is applied to or inserted in the rectum acts as a sedative only after it has been absorbed into the bloodstream. Every case should be painstakingly investigated. Proctoscopy should be a first step in investigating suspected cancer of the lower bowel. Tumours in the ampulla are often inconclusively diagnosed by x-ray examination.

Ambulatory aspect

According to Cantor ambulatory proctology includes in its scope both conservative and surgical techniques such as (1) surgical and injection treatment of haemorrhoids; (2) surgery of most fistulae; (3) pilonidal sinus, cyst and abscess; (4) conservative and surgical treatment of pruritus ani, cryptitis and papillitis; (5) surgery of anal, rectal and perirectal infection and abscess; (6) surgery of benign growths of the anus, rectum and sigmoid; surgical and conservative treatment of fistula in ano; (7) diagnosis and treatment of both specific and non-specific proctitis and sigmoiditis; (8) conservative and surgical treatment of anal stenosis and rectal stricture; (9) surgery of prolapse and most procidentias; (10) fulguration of early malignancy if present below the peritoneal reflection and on the posterior rectal wall. Local analgesia with an oil-soluble anaesthetic affords the prolonged action necessary for ambulatory patients, in whom postoperative oedema is less prominent and less often found than it is in hospital patients. In dealing with haemorrhoids adequate local analgesia is essential for adequate sphincter relaxation and exposure of operative field. The author obtains it by initial procaine infiltration of perianal skin and sphincters followed by infiltration with oil-soluble anaesthetic solution. Pain, even after the most extensive surgery, is very rare. Cantor prefers the technique of clamp and ligature. Procaine analgesia suffices for treatment of all but the most complicated of fistulae. The treatment of these should be surgical; sclerosing agents should not be employed. Complete excision under local analgesia is indicated for fistula in ano. Local analgesia is satisfactory for draining the perirectal abscesses which usually complicate cryptitis. As a fistula may extend from the involved crypt, incision should be as near as possible to the anal verge.

Surgical sponges

Use of corn-starch

Bice, MacMasters and Hilbert describe the preparation of sponges by the autoclaving of a 5 per cent suspension of corn-starch, which has been pasted beforehand by heating, for 15 minutes at 15 pounds per square inch gauge pressure. The autoclaved paste is then slowly frozen in shallow pans at a temperature of just below 0° C. After the paste has been allowed to thaw, the resulting sponge can be cut as required. Sponges of different textures result from varying the conditions under which the starch is pasted and frozen. Sterile sponges are obtained by autoclaving and completing the process under aseptic conditions, or by immersing the final product in 70 per cent alcohol, which also toughens it. Starch sponges absorb up to 18 times their own weight of aqueous or alcoholic solution and retain the liquid during gentle handling. If air-dried at temperatures up to 105° C., they return rapidly to their original soft state when they are remoistened. They disintegrate slowly in water. Medicaments such as sulphathiazole can be introduced by various methods and retained. The fact that 100-milligram portions of dried sponge disperse in 4-7 hours at 37° C. in Seitz filter-sterilized beef serum buffered to a hydrogen ion concentration of 7-7.6, suggests that starch sponges used as internal surgical dressings would be dissolved and absorbed by the body, with consequent slow release of the medicament.

Psychosomatic disturbances

Fatigue and the gastro-intestinal tract

Portis discusses the medical treatment of psychosomatic disturbances, with special reference to the gastro-intestinal tract and to fatigue. Although many of the symptoms complained of by the patient may be due to altered functions resulting from emotional disturbance, a thorough clinical and laboratory investigation should always precede a psychological one. That the gastro-intestinal tract is easily affected by emotional disturbances is partly due to its abundant afferent and efferent nerve supply and partly to the very important emotional part which, from the individual's earliest days, is played by eating. After organic disease has been eliminated, gastritis, dyskinesia of the biliary tract, gaseous disturbance of the small intestine with colicky and cramp-like pains, segmental spasm and rapid motility, may be found to be due to emotional stimuli. Rapid emptying of the small intestine may cause some of the vitamin imbalances, as well as iron deficiency anaemias and disturbed protein and electrolyte balance. The colon may be the receptor of altered emotional stimuli; even ulcerative colitis may have associated emotional factors. There is often a large psychodynamic factor in duodenal and simple gastric ulcers, and psychotherapy combined with medical measures is valuable. The danger of malignancy in chronic gastric ulcers must not be forgotten. Emotion-

ally disturbed patients may experience fatigue, which appears in the early morning and late afternoon often with severe headache. These patients give a flat curve when they are tested by an intravenous glucose tolerance test and the fatigue would appear to be due to relative hypoglycaemia. Diet is very important and should be essentially high in protein, moderately high in fat, and relatively high in carbohydrates. Frequent meals during the day are necessary and an extra one on retiring at night. Atropine has been found to raise the blood sugar level, and should be given 3 times a day and at bedtime. On this regimen and with psychiatric treatment as well patients improve greatly.

Rest

Dangers of rest in bed

Dock considers the evil sequelae of complete rest in bed. These are more likely to occur in elderly obese patients who are being given sedatives than they are in young and lively persons who do not require sedatives. Normal sleep is associated with frequent changes of position, except in cases of shock, pain or prostration. When the shoulders are propped up as in Fowler's position, the veins of the pelvis and of the hips are dilated and the velocity of blood flow is decreased. Veins which are compressed and empty on account of pressure may suffer endothelial damage and begin to thrombose while still nearly empty. During a sudden rise in venous pressure as in coughing or expulsion of faeces, loosely adherent clots may be dislodged and propagated far along the systems. Those patients who get up or have a severe cough or any condition which causes air hunger or impaired blood coagulation, are less subject to serious vascular accidents, since the clots are dislodged before they become of significant size. In these patients there is not the tendency to collapse of alveoli and subsequent hypostatic pneumonia which is so common in those with heart failure or passive hyperaemia. Necrosis is more likely to occur after pulmonary embolism and infarction in a collapsed lung than it is in an aerated lung. Infarction may ensue after pulmonary embolism in cases in which there is no heart failure. Over-sedation and limitation of movement predispose to occurrence of infarcts. Measures which minimize the hazards of complete rest include warning the patient against Valsalva's experiment ('bearing down') while supine, the omission or restriction of narcotics, deep-breathing exercises and constant changes of posture.

Feeding methods

Use of Ryle's tube for intragastric administration of fluids

Ransome, Gupta and Paterson report on the successful use of Ryle's tube for the intragastric administration of food, fluids and drugs to patients who are too feeble to drink. A large quantity of fluid can safely be absorbed from the alimentary tract, except in cases of hypoproteinaemia. Therefore the method is valuable in the treatment of dehydration in the Tropics where fluid loss is often to be measured in gallons. There is no risk of causing pulmonary oedema and the procedure may be safely adopted in patients with acute pulmonary disease. The patient is supported in the sitting position and the lubricated tube is passed transnasally for 6-8 inches. Coughing and retching ensue, the patient swallows and the tube is drawn into the oesophagus. Finally the tube is pushed into the stomach where it may remain for as long as 3 weeks without ill effect. Should the swallowing reflex be absent, the tube must be guided into the oesophagus by means of the fingers. A preliminary hypnotic is required for refractory patients. Evidence was not found either of ulceration of the laryngopharynx or of aspiration bronchopneumonia in a series of 355 acute medical cases.

DRUG GROUPS

Anthelmintics

Synthetic lactones

Paranjape and his colleagues record observations *in vitro* on the anthelmintic action of some synthetic lactones and compounds allied to santonin. The anthelmintic property of a drug is due to the phenolic-hydroxyl group and the benzenoid part of the molecule. It has been shown that angelica lactones and their derivatives with aromatic aldehydes are good anthelmintics, their action being due to the lactone group. The aim of the authors' observations was to find out which amongst a number of synthetic products are capable of being used as good anthelmintic drugs. In place of parasitic roundworms, earthworms were substituted and were immersed in 100 cubic centimetres of solutions of the substances. The time intervals for the loss of activity of the worms and for death to occur were recorded in minutes and so were control immersions in 0.02 per cent solution of santonin. The toxicity of the synthesized products was also tested against young small freshwater fish. Synthetic santonin and a related compound with a methyl group were found to be equally toxic to fish and to earthworms. Substances containing the dione structure, as in santonin, but not the lactone ring, were all toxic to earthworms and to fish but the simple diones in which the angular methyl group appears to increase the anthelmintic action are comparatively more toxic. Desmotroposantonin was not toxic to either fish or earthworms. All phenolic compounds proved to be highly toxic to earthworms, rapidly attacking the skin which peeled off. Tetrahydro naphthols were less toxic than were santonin and the diones. The results of experiments with butyrolactones show that activity is greatest when the isobutoxy group is introduced. Most of them attack the skin of the earthworms and thus indicate that they are unsafe to use as drugs. The butyrolactone structure has importance in imparting toxic properties to such substances as the free phenolic group in the benzene ring.

Antispasmodics

Pancreatic extracts and the smooth muscle tissue

Dreisbach, Van Winkle and Hanzlik describe experiments the results of which refute the claims made for the value of certain pancreatic extracts in the treatment of angina pectoris, intermittent claudication, various symptoms of peripheral arterial disease, ureteral colic and dysmenorrhoea. The two substances tested were the pancreatic extracts, free from insulin, histamine and choline, known as Padutin and Depropanex, which are claimed to have an antispasmodic action due to direct inhibition or depression of involuntary muscle. Two hundred and thirty tests were made on 55 specimens of circular muscles of the abdominal aorta, common carotid and femoral arteries, longitudinal muscle of small intestine, circular muscle of ureter and strips of bladder fundus of dogs or rabbits. Functional activity was tested by application of epinephrine (adrenaline) to arteries and acetylcholine to other tissues and the results with those not reacting typically were rejected. Padutin, in concentrations over 400 times the dose recommended clinically, exerted no more effect than did its preservative, glycerin, alone. Depropanex itself, apart from the effect of its preservative—0.25 per cent phenol—stimulated arterial and bladder muscles but had not any effect on normal or excited intestinal or ureteral muscles.

Cardiac drugs

Electrocardiographic records

Tandowsky, Anderson and Vandeventer report on the effects of various so-called cardiac drugs as seen in the electrocardiogram. Each preparation, in the full digitalizing dosage recommended by the manufacturer, with one exception was given intravenously to two subjects with healthy cardiovascular and renal systems. Each subject had an electrocardiogram recorded in the four conventional leads, the machines used being standardized so that a deflection of 1 centimetre represented a potential difference of 1 millivolt. After the drug had been given, the patient being supine, lead II was recorded at 10-minute intervals for not less than 2 hours. Both Cedilanid and Digoxin (preparations of glycosides from *Digitalis lanata*) produced gradual depression of the RS-T segment, beginning at 10 minutes; in the case of Cedilanid the depression reached a maximum of 2 millimetres at 100 minutes and in the case of Digoxin, of $\frac{3}{4}$ millimetre at 120 minutes; return of the segment to the normal occurred with the first drug within 24 and with the second within 8 hours. Cedilanid caused diminution of the T wave which became iso-electric at 80 minutes and remained thus for 24 hours. Digoxin produced a T wave depression of $\frac{1}{2}$ millimetre at 120 minutes. Neither drug had much sinus effect. Freshly prepared Ouabain (one sample used proved to be inert) produced sinus reduction of heart rate from 92 to 52 per minute at the end of 130 minutes. The maximum depression of 1 millimetre of both RS-T segment and T wave occurred at 10 minutes. By the end of 120 minutes both components had regained their positive polarity to two-thirds of the normal. Digalen and Digilanid caused slight depression of both components and moderate sinus reduction of heart rate. Neither strophanthin-K, Strophosid, Scillaren-B nor Coramine (nikethamide) had significant electrocardiographic effect. Metrazol (leptazol) given subcutaneously produced a 1-millimetre depression of the RS-T segment and a $\frac{1}{2}$ -millimetre increase in positive polarity of the T wave, and caused reduction in heart rate of 25 beats at 120 minutes. The authors consider that the appreciable and characteristic electrocardiographic effects of Cedilanid, Digoxin and Ouabain warrant further investigation.

Vasoconstrictors

Difficulties in nasal conditions

Kully does not believe that there is sufficient justification for the increased use of drugs producing nasal vasoconstriction. These drugs are adrenergic in action but, if vasoconstriction is severe or prolonged, a secondary vasodilatation ensues. The secondary reactions are increased by the addition of antiseptics to the nasal medicaments. Preparations containing sulphathiazole are the prime offenders. The value of vasoconstrictor therapy for acute rhinitis is questionable, because medications which shrink the tissues result in the reversal of the normal response of the nasal mucosa to infection. Persistence of watery secretion and nasal obstruction beyond the third day of an acute rhinitis signifies the presence of after-congestion due to the improper use of medication. The vasomotor rhinitis produced by drugs is identical in appearance with that due to allergy. One patient with nasal obstruction had been given nasal medication and injections against allergy for 30 years. Discontinuance of the treatment produced a permanent cure. The use of vasoconstrictor drugs in chronic nasal obstruction adds the factor of secondary congestion to the obstruction already present. Persistent vasodilatation and oedema may cause obstruction of the orifices of the sinuses, thereby predisposing to acute sinusitis. In a series of 640 cases of acute sinusitis 85 per cent of the patients had used some form of nasal vasoconstriction for 3 or more days prior to the onset of the symptoms. Furthermore, otitic complications may be caused by the congestion around the eustachian orifices or by the entrance of drops into the middle ear.

ALLIED DRUGS

Blood proteins

Therapeutic application

Cohn discusses the application in the future of the knowledge gained from war experiences of the therapeutic effects of blood proteins. Whole blood is necessary when there has been

patients (13.3 per cent) Haematuria occurred 15 times. If deaths in patients moribund on admission are excluded the case fatality rate is 4.5 per cent.

Combined with penicillin

Blake describes the indications for administration of sulphonamides and penicillin. Owing to simplicity of administration the sulphonamides are indicated for the treatment of the less severe haemolytic streptococcal infections with tissue invasion but without suppuration, necrosis or bacteraemia such as erysipelas or lymphangitis, in mild upper respiratory infections the value of sulphonamides is debatable. In severe haemolytic streptococcal infections penicillin often succeeds when sulphonamides have failed, for example in severe cellulitis, mastoiditis with or without intracranial complications, meningitis, pneumonia, empyema, pericarditis, endocarditis, peritonitis, puerperal sepsis, osteomyelitis, suppurative arthritis and infected wounds. In such conditions as empyema, meningitis and arthritis, however, penicillin must be injected locally as well as intravenously or intramuscularly. In very severe pneumococcal pneumonia, especially in the aged, and in other pneumococcal infections such as mastoiditis, empyema, meningitis, endocarditis and peritonitis, penicillin is more effective and should be used initially. Penicillin is indicated for staphylococcal infections, although some strains of staphylococci contain a penicillin inhibitor similar in action to the penicillinase found in colon bacilli. Subacute bacterial endocarditis due to *Streptococcus viridans* responds only temporarily—if at all—to sulphonamides, but large amounts of penicillin, in 3–4 week courses, may induce remissions. In meningococcal infections penicillin is necessary only when sulphonamides have failed or as additive treatment in severe fulminant cases. Penicillin is the more effective agent in gonococcal infections and should be used in all sulphonamide-resistant cases and in all those complicated by arthritis, ophthalmia, endocarditis, pericarditis, peritonitis, epididymitis and prostatitis. Penicillin is ineffective and sulphonamides are indicated in Gram negative bacillary infections. The effects of penicillin on clostridial infection and on syphilis remain to be determined.

INDIVIDUAL DRUGS

Demerol

General clinical effects

Yonkman, Noth and Hecht describe the pharmacological and clinical effects of Demerol (Pethidine hydrochloride), a synthetic drug chemically allied to morphine and to atropine and of analgesic, spasmolytic and sedative action. It is a white insoluble crystalline substance, soluble in water as the hydrochloride, slightly bitter, and non-irritant to the gastro-intestinal mucosa. Experiments showed it to be safe and non-toxic even in large doses, it is readily absorbed when given subcutaneously, intramuscularly or by the mouth and has a sedative and analgesic effect. The intestinal stimulation produced by it in dogs was absent in man. In clinical studies by Noth, Hecht and Yonkman 146 patients were observed. 118 had severe acute or chronic pain and 4 bronchial asthma, 24 patients without pain were studied for the sedative effect of the drug. The type and the severity of the pain were noted as well as its duration, the effect of previous medications and the subjective and objective response to individual doses of demerol, a summary was made of the analgesic and sedative effects and of the side-effects. In patients who were treated for longer periods with the drug complete urine analysis and blood studies were made weekly, electrocardiograms and bromsulphthalein tests of hepatic function were performed frequently to discover evidence, if any, of toxicity. The usual dose given was 100 milligrams, orally or intramuscularly, and in 123 instances of severe pain occurring in 118 patients complete relief was obtained in 64.2 per cent, partial relief in 23.6 per cent and no relief in 12.2 per cent. The study of the sedative effect of Demerol showed production of sleep in 50 per cent of cases, mild sedation in 30 per cent and no effect in 20 per cent. Three asthmatic patients were benefited and one was not. Side-effects such as vertigo, nausea and vomiting were noticed in 27.4 per cent of patients, but only in 4.8 per cent was it necessary to stop administration of the drug. In conclusion, Demerol may be considered to be an effective relatively non-toxic analgesic drug with less addictive properties than has morphine and its derivatives, and to be capable of being used instead of them in many different painful conditions.

In treatment of chronic arthritic pain

Batterman describes the results of a study of Demerol (Pethidine hydrochloride), one of the newer synthetic analgesics, used for the treatment of chronic arthritic pain. During 4 years from March 1941, 183 hospital patients and 73 out-patients in New York were treated with Demerol either parenterally or orally, in doses of 50, 75 or 100 milligrams. It was found that regardless of diagnosis, severity of pain or dose satisfactory analgesia was produced in 83 per cent, and moderate relief in an additional 13 per cent, when the analgesic was produced parenterally, and that oral administration gave relief in 62 per cent and moderate relief in 18 per cent of cases. There were few or no untoward reactions, and provided the drug was given at regular intervals, prolonged administration, even for weeks or months, gave the same satisfactory results. These were also obtained, regardless of causation, in cases of myositis, acute bursitis, advanced osteoarthritis, rheumatoid, gonococcal and non-specific infective arthritis, and in the pain of the sciatic syndrome. Only in the polyarthritis due to rheumatic fever were the results unsatisfactory only 9 out of 18 trials having given relief of pain. With

ambulatory patients it is necessary to begin with a small dose of Demerol, 25 milligrams for the first few days, until the tendency to untoward reactions, dizziness, nausea or vomiting subsides, after which the same favourable results as those seen in hospital cases are produced. In the relief of severe longstanding pain the advantages of Demerol, as compared with morphine, are its minimal danger of addiction and its undiminished effect without increased dosage.

Flavine

Tests for efficacy on the skin

Bonney and Allen in discussing the sterilization of skin state that in 1918 Bonney and Browning introduced violet green solution, a non-irritant antiseptic with a high bactericidal power. Its main drawback is that it deeply stains hands and bed linen. In place of violet green solution, the authors have recently used a pale lemon-tinted solution of 1 per cent colourless flavine (5-aminoacridine) in equal parts of water and rectified spirit. The spirit acts as a grease solvent and the water is necessary in order to permit full antiseptic action. Six hours before operation the solution is painted on the cleansed area of skin, covered with lint soaked in the solution and protected with a waterproof material and a binder. The efficacy of the solution was tested in 38 consecutive cases by means of cultures on blood agar from a platinum loop streaked over the prepared skin surface immediately before operation. A control of 38 plates was made from unsterilized areas. Of the 38 plates from prepared areas 29 did not show any growth after 4 days and 9 did show growth, whereas all plates from the control areas showed growth. The commonest organism identified was *Staphylococcus aureus haemolyticus* and the authors emphasize the importance of the destruction of this potent source of infection by means of efficient sterilization.

Lanatosid C

In different cardiac conditions

Erickson and Fahr describe the effect upon the heart of lanatosid C in 39 patients with organic cardiac disease. The series consisted of 9 cases of rheumatic heart disease, 20 cases of hypertensive heart disease, and 10 cases of coronary arteriosclerosis. These patients had normal venous pressures and circulation times. There was no evidence of congestive heart failure. Each patient was given lanatosid C in a dosage of 0.5 milligram 6 times daily for 2 days. Subsequently the maintenance dosage varied between 0.5 and 1 milligram daily. For purposes of comparison 14 normal subjects received similar treatment. Tests of cardiac function were made before and after administration of the drug. The investigations included kymographic studies, effort tolerance tests, and measurements of the circulation time by the calcium gluconate arm-to-mouth method. It was apparent that lanatosid C increased the mechanical efficiency of the hearts of most of the patients with organic cardiac disease, whereas the drug decreased the mechanical efficiency of the normal heart. Therefore glycosides of digitalis are toxic to normal hearts but are beneficial to most abnormal hearts. In the normal heart digitalis in full dosage decreases the percentage of energy converted to circulatory work. The heart empties itself less completely and, in consequence, the systolic volume is increased and the stroke output is decreased. The opposite effect is produced in the abnormal heart. The degree of improvement in mechanical efficiency in cases of compensated cardiac disease was correlated with the circulation time. It was greatest in cases in which the circulation time was 16–20 seconds. In all cases the mean increase of vital capacity was only 2 per cent. Subjectively, the majority of patients with compensated heart disease did not note any change while digitalis was being administered, but a few patients stated that physical exertion did not exhaust them as rapidly as it did before the commencement of treatment. Improvement was not maintained in 18 patients examined 6 months after discontinuation of the drug. In 50 per cent of these cases the heart was less efficient than it had been before treatment.

Penicillin

considerable blood loss, or when it is anticipated in surgical procedures, because the therapeutic effects of erythrocytes depend upon their oxygen carrying function. The lability of whole blood has necessitated accumulation of reserves of more stable components of blood. Investigation is urged of the further possibilities of the use, for reasons of economy, of cells and plasma separately. Separated plasma can be stored as a liquid or frozen or dried from the frozen state. As liquid it retains its colloidal anti shock properties but its more labile components, such as prothrombin, fibrinogen complement and antibodies, deteriorate with time. In the frozen and dried states most of the labile components are preserved. Injected plasma proteins increase the body's reservoir of proteins and increase the plasma volume by drawing water from the tissues into the blood stream. Although all dissolved colloids exert some osmotic effect, the smaller proteins of the blood stream—the albumins—control the equilibrium between the water and the electrolytes in blood and tissues, the albumins represent less than 60 per cent of the plasma proteins but produce 80 per cent of the osmotic effect so valuable in the treatment of shock. Iso-electric salt-free albumin is prepared as a white powder which can be redissolved at any concentration in any diluent. Experiments have demonstrated the efficiency in prevention or modification of measles, of the more soluble fraction, known as pseudoglobulin or fraction II, of serum globulin. Experiments are proceeding concerning the elimination of depressor substances which have hitherto prevented the intravenous administration of globulin concentrates and with the separation of globulins from iso-agglutinins. The use in haemostasis of thrombin in a matrix of fibrin foam is described. Fibrin foam is a porous material composed of strands of fibres separated by air spaces of macroscopic size and is formed from fibrinogen and thrombin, it effectively controls bleeding from oozing surfaces and large veins. Although its use is not advisable for treatment of brisk arterial haemorrhage its effects are excellent in neurosurgery.

Hormones

Steroids rate of absorption

Shimkin and his colleagues report on experiments demonstrating that the decreased rate of absorption of a subcutaneously implanted steroid hormone is attributable to the manner in which the surface area of the pellet changes with alterations in volume. Each pellet was cylindrical in shape, with the diameter equal to the length. Sterility was ensured by using pellets prepared by fusion rather than by compression. Preparations of stilboestrol were inserted into the subcutaneous tissue of adult male mice. At varying intervals the pellets were removed, freed of connective tissue, dried and weighed. These preparations were then implanted into other mice of the same strain and sex. It was found that the formation of a connective tissue capsule had not any effect on the quantity of hormone absorbed. Mathematical analysis showed that the absorption of the pellets is a function of the surface area. With a gradual reduction in the size, the rate of absorption decreases because the surface area is reduced. In order to maintain an approximately constant level of dosage for a protracted period it is necessary to repeat the implantations so as to compensate for the amount absorbed. The technique may prove to be of value in the administration of testosterone propionate and desoxycorticosterone acetate. It should be possible to adopt the method in the treatment of women with oestrogens, thus allowing the reproduction of the normal cyclic quantities of oestrogens shaped into pellets small enough to pass through a hypodermic needle.

Salicylates

Fatal reactions

Ashworth and McKemie describe 2 cases of rheumatic fever the fatal results of which were apparently due to treatment with salicylates. The first patient a white woman aged 20 years, was admitted to hospital with acute rheumatism, she had no heart affection and was not acutely ill. After large doses of sodium salicylate—10 grammes daily for 6 days—the joint swelling and pain disappeared but mental symptoms developed, with attacks of hyperpyrexia and hyperpnoea, and the patient became comatose and died. Post mortem examination showed no inflammatory lesions in the central nervous system but there were generalized acute hyperaemia and focal haemorrhages. In the second case, that of a negro boy aged 4 months after a comparatively large dose of acetylsalicylic acid had been taken, hyperpnoea, hyperpyrexia and convulsions developed. After death, haemorrhages were found in various parts of the body, particularly in the brain, and severe widespread hyperaemia, but there was no evidence of an inflammatory disease. The cause of these findings is considered to be a combination of capillary damage and hypoprothrombinaemia produced by the salicylates. Vitamin K, which experimentally has been found to prevent hypoprothrombinaemia, should always be given when large doses of salicylates are used.

Sulphonamides

Criteria of effectiveness

Whitby considers that the criterion of the effectiveness of a sulphonamide compound depends upon its ability to substitute in bacterial metabolism for *p*-aminobenzoic acid. For this reason the sulphonamides have no therapeutic action on the common virus diseases. The drugs must be administered regularly and in full dosage otherwise the bacteria may be given the chance to multiply freely. Whenever possible the oral route should be used in preference to the giving of injections. The first dose is relatively large and is followed by maintenance doses given

and bacteriological reports are helpful. Apparent failure should call for investigation to make sure that there is no dead tissue, that penicillin is reaching the site of the infection and that the dose is adequate. Finally, the infecting bacteria may be insensitive to the drug or the preparation may have lost its potency.

Description of its properties

Florey observes that a long history of research preceded the discovery of penicillin in 1940 and dates from the observations of Pasteur and Joubert in 1877 on naturally occurring antibacterial substances. In 1928 Fleming recognized the value of the antibacterial powers of the penicillin which he had discovered, but the first stable products containing penicillin were produced at Oxford and there its chief chemical and therapeutic properties were investigated. The bacteria sensitive to penicillin are—*Streptococcus pyogenes*, *Streptococcus viridans*, *Diplococcus lanciolatus*, *Staphylococcus aureus*, *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Actinomyces bovis*, *Clostridium perfringens*, *Clostridium septicum*, *Clostridium oedematiens*, gonococcus and meningococcus. Most of the Gram negative bacilli and *Mycobacterium tuberculosis* are insensitive. Pure penicillin was found to be bacteriostatic in solutions as dilute as 1 in 50 000 000, its activity is maintained in serum and pus, and in the presence of autolysed body tissues. It inhibits the growth of bacteria whether they are present in large numbers or in small, and it has practically no toxic effect on animals. Destroyed when given by the mouth or rectum, it is readily absorbed when injected into skin or muscles, and is quickly distributed round the body. Clinical trials soon implemented the promise that penicillin was a true chemotherapeutic agent. Attempts are now being made to synthesize the substance, its manufacture from the mould has been very largely increased, although supplies are still insufficient. The curative properties of penicillin have been further explored. Treatment by injection invaluable in septicæmic and deep seated conditions has the disadvantage that penicillin is rapidly excreted by the kidneys and therefore has to be used in large amounts. The only other method—that of local application, can be undertaken only if every portion of the infected tissues is made accessible to the substance and much scope is thus left for the ingenuity of the surgeon. Perhaps the most striking recent development is the American discovery that penicillin is apparently effective in syphilis. Another excellent use is in the prevention of serious sepsis, especially in battle casualties.

General therapeutic properties

Fleming¹ considers that penicillin is very rapidly absorbed after intravenous, intramuscular or subcutaneous injection, but absorption may be slow from the diseased pleura and from abscess cavities. Scarcely any time is saved by administering penicillin intravenously, since it is at its maximum in the blood within 15 minutes of an intramuscular or subcutaneous injection. Absorption is slow from joints and from the cerebrospinal cavity. In most types of meningitis the drug is best used both systemically by parenteral injection and locally by intrathecal injection. The oral route has not yet proved to be satisfactory, for the preparation is destroyed in the stomach. Penicillin is rapidly excreted by the kidney, but smaller amounts appear in the saliva, sputum and bile. No serious toxic effects of penicillin have been recorded, but phlebitis and clotting may complicate the intravenous drip method. Painful reactions after intramuscular or subcutaneous injections can be diminished by dissolving the drug in saline with procaine. There is little benefit to be obtained if the drug is used for infections caused by bacteria insensitive to penicillin. Systemic penicillin treatment is effective in cases of pneumonia, carbuncle, staphylococcal septicæmia and acute osteomyelitis. The drug will cure gonorrhoea in a few hours, and it is likely that patients can recover from syphilis after one week of treatment. Prophylactic penicillin is useful in military surgery, especially in cases requiring operations through infected tissues. For local treatment the drug can be dispensed in the form of a cream, ointment, powder or gelatin lozenge. Calcium penicillin is less deliquescent than is the sodium salt of penicillin and is thus more suitable for powders and snuffs. A local application of 2 000 units may be enough to cure a small superficial lesion. In systemic diseases the dosage varies from 100 000 units for acute gonorrhoea to 10 000 000 units for subacute bacterial endocarditis.

Optimum methods of administration

Herrell, Nichols and Heilman consider that the use of penicillin therapy should be confined to institutions so long as it has to be administered intravenously or intramuscularly. The continuous intravenous drip method best maintains a constant level in the blood and this level can be reliably determined by Fleming's test. A daily dosage of 100 000 units is probably maximal for the treatment of common infections. In cases of venous irritation the intermittent intramuscular method may be employed but the dose must be doubled if satisfactory results are to be produced. Local irritation due to the injection can be minimized by changing the product or the site of administration. Febrile reactions may occur if the preparation of penicillin contains pyrogens and, in the presence of cutaneous sensitivity, treatment must proceed with caution. Penicillin does not pass from the blood into the spinal fluid, and supplementary intrathecal instillations are required for the treatment of meningitis. Local instillations are efficacious for suppuration in the chest or the joints but subcutaneous administration produces variable results. Both the sodium and calcium salts are used for local treatment but the calcium salt is the more satisfactory. Penicillin is transmitted through the placenta to the fetus and this fact provides a rational basis for employing the preparation in the treatment of ante partum syphilis. Twenty four organisms are known to be susceptible to the action of

penicillin of equal inhibitory power. By some means penicillin in passing through the body increases in stability. The anti bacterial substance in such urine is more resistant to changes in hydrogen ion concentration and to heat than is a comparable solution of penicillin. It has been held that penicillin given by the mouth will be destroyed by the gastric juice, and that only large doses would be beneficial. It has now been found that the more complex diluents of penicillin such as milk and cholesterol give better results than do simple ones such as water and broth. Several volunteers swallowed 15,000 units in saline 3 hours after breakfast and penicillin was found in the urine for some hours afterwards in all but one who was found to be suffering from hyperacidity of the gastric juice, his urine showing no inhibition, when it was administered intramuscularly penicillin appeared in his urine. The most satisfactory results occurred when this volunteer was given an alkali—a teaspoonful of sodium bicarbonate, and then penicillin mixed with raw egg. An excretion in the urine of 75–80 per cent ensues after both parenteral and oral administration but persists for a longer period after oral administration. The blood serum level of bacteriostatic activity proved to be satisfactory after oral administration preceded by the giving of an alkali.

McDermott, Bunn, Benoit, Dubois and Haynes have investigated and are continuing to investigate the results of oral administration of penicillin. Twelve patients so far have been thus treated for pneumococcal pneumonia, the effects are comparable with those of intramuscular injection, but five times as much oral penicillin is necessary to attain an equal serum concentration. In studies on normal subjects, the following were given on successive days (1) penicillin in corn (maize) oil, (2) penicillin in 30 centimetres of water, (3) penicillin in water 3 hours after administration of a 4-gramme dose of magnesium silicate (precipitated) as a buffering agent and (4) penicillin in peanut oil (arachis oil) and 4 per cent beeswax. The subjects fasted throughout the period of observation. After ingestion in the media described above of 315,000 units of penicillin orally, serum concentrations varying between 0.312 and 1.25 units of penicillin per cubic centimetre were found 30 or 60 minutes later. Duration of penicillin action appears to be prolonged, as it is in intramuscular administration, by the use of oil in beeswax media. Total urinary excretion of penicillin during the 12 hours after ingestion by all four methods was, in the majority of cases, approximately 12 per cent.

Oral administration in various conditions

Gyorgy and his colleagues state that penicillin given by the mouth is absorbed by the gastrointestinal tract. Twenty three patients with gonorrhoea were given penicillin in combination with trisodium citrate, orally. The total dosage of penicillin ranged from 240,000 to 480,000 units. In all cases cure was achieved in 1–3 days with doses comparable to the customary quantity of penicillin given by injection. Oral medication also produced successful results in gonorrhoeal conjunctivitis and in streptococcal vaginitis. A patient with early acquired syphilis was given 30,000 units of penicillin and 5 grammes of sodium citrate by the mouth every 3 hours. In 30 hours the dark-ground examination was negative for *Treponema pallidum*. Sulphathiazole therapy was of no avail in a child suffering from chronic otitis media with perforation and suppuration. Oral administration of 10,000 units of penicillin combined with 2 grammes of sodium citrate every 3 hours brought about the complete disappearance of otorrhoea. In a series of experiments penicillin and sodium citrate were given by the mouth 30 minutes before breakfast. Blood tests for penicillin were based on the inhibition of haemolysin production by a selected strain of streptococcus. It was found that the buffer salt increased the absolute blood levels and also prolonged the presence of penicillin in the blood. Penicillin could be detected in the blood 4 hours after ingestion, whereas it is a rarity to find the drug in the blood even 3 hours after intramuscular injection of an aqueous penicillin solution.

Oral administration in oil

Libby describes oral administration of penicillin in oil. The various salts of penicillin are inactivated by gastric acidity but all penicillin activity is not lost in the stomach. It has been proved that the drug can be absorbed from the small intestine. Administration in tablets with an enteric coating or simultaneously with antacids, having been adversely reported on the author, exploiting the facts that little if any fat splitting takes place under the acid conditions of the stomach and that most of the breakdown and digestion of fats occur in the small intestine, experimented with oral administration of sodium and calcium salts of penicillin in suspension in cotton-seed oil which had been proved to be the best oily medium. Suspensions of 150–300 units of penicillin per milligram were dispensed in gelatin capsules made up to contain 10,000, 25,000 or 50,000 units per capsule. Approximately 90,000 units of sodium penicillin were administered to a man weighing 86 kilograms. Urine examination 25 minutes later showed 0.4 unit of penicillin per milligram. Maximum urine penicillin was found during the first 2 hours after ingestion the level then gradually decreased to 1.8 units per milligram 8 hours after administration. Blood levels were approximately 0.05, 0.04, 0.04, 0.02 and zero ingestion.

Precautions in local application

McKissock, Logue and Bartholomew urge the need for asepsis in local penicillin therapy, particularly in neurosurgery. Gram negative organisms which are penicillin resistant, have been found in the discharge from wounds treated with penicillin. The presence of these organisms is an example of hospital or cross infection of wounds. Their entry to the wound occurs when injections of penicillin are made through the rubber tube which is inserted into

the depths of the wound for the purpose of giving passage to the solution. The *Escherichia coli*, *Proteus vulgaris* and *Pseudomonas aeruginosa* can all cause meningitis or localized abscess. An aseptic screw cap was therefore devised to close the penicillin tube. A potential source of infection to the stab wound after the tube is withdrawn is the healed linear wound and the surrounding scalp. Observations were carried out on two series each of 20 cases. Bacteriological examinations were made before operation and up to 5 days postoperatively. The first series was taken from a unit in which there was an adequate, well trained and experienced nursing staff. In the unit from which the second series was taken, the staff was insufficient, were inexperienced in neurosurgical work, and had not had much training in hospital infection. The potential cross infection in the first series was 3 cases in 20. There was no clinical cross infection. In the second series the potential rate was 7 cases in 20 and one case of superficial clinical hospital infection arose. It is suggested that the use of the aseptic screw cap in these series prevented cross infection of the wounds by way of the penicillin tube. The need for proper closure of a scalp wound and early skin healing is emphasized in view of the total average potential cross infection rate of 25 per cent for both series.

In diseases of the ear

Swanson and Baker discuss the use of penicillin in diseases of the ear, stating that it is particularly suitable for these cases since both local and systemic administration can be undertaken, and that probably about 90 per cent of organisms causing acute infections of the ear are penicillin-sensitive. The authors state that in 14 cases of acute otitis media all the patients responded successfully to total doses of penicillin of between 360,000 and 1,140,000 units given intramuscularly during 5-15 days. In another case reported on in detail penicillin was started 16 days after the onset of the illness when sulphonamide therapy had failed and mastoidectomy seemed to be necessary. The patient was cured in a fortnight, having received 2,260,000 units. Simple mastoidectomy was performed on another patient with acute mastoiditis. At the conclusion of the operation 15 cubic centimetres of penicillin solution, containing 1,000 units per cubic centimetre, were injected into the closed mastoid cavity through a rubber drain, the end of which was sealed by gauze impregnated with penicillin. Further injections of 3 cubic centimetres of solution were given at 6-hourly intervals and 30,000 units of penicillin were given concurrently every 3 hours intramuscularly for 3 days; the local injections were then stopped and the intramuscular injections reduced to 15,000 units for a further 4 days, when a total of 1,905,000 units had been given. The wound healed on the eighth day after operation. A case of acute labyrinthitis was successfully treated with 455,000 units of penicillin given by continuous intravenous injection, although a total loss of hearing on that side remained. Swanson and Baker describe the treatment of a case of chronic otitis media with a large perforation of the drum; penicillin was introduced locally by repeated injections of a solution of the drug through the perforation into the middle ear, through a pneumatic otoscope, and the ear was afterwards sealed with cotton impregnated with a bland ointment. In one other similar case, the treatment was successful but in several others there was not a satisfactory response.

In gas gangrene and allied conditions

Fisher and his colleagues discuss the effect of penicillin on the incidence and course of gas gangrene and allied conditions. Observations were made on nearly 4,000 battle casualties. Penicillin injections were given in 11 per cent of the cases, since it was thought that in these patients gas gangrene would be most liable to develop. The initial dosage was 100,000 units, and 45,000-50,000 units were given 6 hours later. The latter dose was repeated at intervals of 4 or 5 hours until the operation was performed. No instance of gas gangrene occurred in the patients given prophylactic penicillin, whereas the incidence of the disease in the remainder of the cases amounted to 0.14 per cent. Good results were obtained in the treatment of local gas gangrene. This treatment included the injection of gas gangrene antiserum, the intramuscular administration of penicillin for 10-15 days, and the local application of penicillin paste. Wide incisions were made, and necrotic muscle was removed. All wounds were healed at the end of a period ranging from 4 to 14 weeks. Bacteriological findings supported the clinical diagnosis. It was found that clostridia persisted even when the wound surface was clean. The organisms were present, however, for a period approximately equivalent to the duration of muscle swelling. It appears that clostridia can be solely responsible for wound sepsis. Moreover, in cases treated with a short or interrupted course of penicillin, the organisms may produce a severe toxæmia without local signs of gas gangrene. In these circumstances diagnosis becomes difficult and the patient may not receive the benefit of antiserum or of further chemotherapy. The toxæmia may be accompanied by a high rate of blood urea. The authors detected a blood urea of over 50 milligrams per 100 cubic centimetres in 8 of 23 cases of clostridial wound infection.

In diseases of the male genito-urinary tract

In a paper read before the Urology Section of the American Medical Association, Thompson deals with the use of penicillin in 500 cases of gonorrhoea and 100 cases of other infections of the male genito-urinary tract. In most cases the sodium salt was used, but the calcium salt, when used, seemed to be identical in action. At first the penicillin was given by continuous intravenous drip, 1 litre of isotonic solution containing 20,000 units being given every 12 hours, night and day, for 96 hours; this gave good results, as did also a reduced dose of 80,000 units in 12 hours, but both caused nursing difficulties. Injections of a solution con-

taining 5,000 units of penicillin per cubic centimetre into the gluteal or deltoid muscle was found to be the ideal method of administration. The injection of 20,000 units every 3 hours, continued for many doses, did not cause any irritation, a stronger solution of 10,000 units per cubic centimetre caused pain. Injections of 20,000 units each given every 3 hours, up to a total of 100,000 units gave 98 per cent of cures. Intra-urethral administration was tried but did not result in permanent cure. Penicillin was also found to be useful in the treatment of various non-specific genito urinary infections and dealt successfully with penicillin sensitive organisms. For mixed infections other remedies were needed as well. Since penicillin is unstable in solution, soon losing its antibacterial power at room temperature, solutions should be freshly prepared and should be kept in an ice-box between injections. Penicillin is devoid of toxic reaction and complicated methods are not necessary in its use. By making repeated Gram's stains of the urethral or prostatic secretions, or of the sediment of centrifuged urine, the results of treatment in urological cases can be easily determined.

Use in infections after failure of sulphonamides

Harford and his colleagues describe the use of penicillin in the treatment of 103 patients with infections, especially bacterial disorders, unresponsive to sulphonamide chemotherapy. No significant toxic reactions were observed. Systemic treatment was accomplished by means of intravenous or intramuscular injections of the sodium salt of penicillin in doses varying from 5,000 to 40,000 units. In addition, all accessible infected foci were treated by local injections of the drug. Infected wounds were dressed with gauze packs saturated in penicillin solution containing 1,000 units per cubic centimetre. Intrapleural injections of 5,000–20,000 units every 24 hours were used in the treatment of pleural infections. The initial intrathecal dose employed in the treatment of meningitis was 20,000 units. Penicillin therapy was successfully used in 14 cases of staphylococcal bacteraemia. One patient was a child with pericarditis, multiple skin pustules and an abscess of the heel. Surgical drainage of the abscess and intensive penicillin treatment resulted in complete recovery. Death occurred in a patient with cavernous sinus thrombosis, and the treatment was also unsuccessful in a case of bacterial endocarditis. In 2 other cases of acute bacterial endocarditis, however, the patients were well after 2 months and 4 months, respectively. The drug was used in 3 cases of subacute bacterial endocarditis. One patient died, but more than 2 months later the other 2 patients showed no evidence of recurrence. Six patients with acute osteomyelitis were benefited by the drug, but the therapeutic response was less encouraging in chronic cases. Nevertheless, it seems to be likely that the use of penicillin will make patients with chronic osteomyelitis better subjects for surgical procedures. There were 9 cases of pneumococcal meningitis and improvement occurred in all but one of these patients. Successful results were ensured by surgical drainage of infected foci and by continuing penicillin therapy for some time after the signs of meningitis had subsided. Recovery ensued in 4 of 6 cases of pneumococcal pneumonia, but inconclusive results were obtained in 3 cases of empyema. Twelve women with gonorrhoea resistant to sulphonamides were promptly cured with penicillin in doses which, in most instances, did not exceed a total of 75,000 units. The drug was ineffective in the treatment of brucellosis, cryptococcal meningitis, histoplasmosis, actinomycosis and ulcerative colitis. One patient with meningococcal meningitis was cured in spite of the fulminating character of the infection, but persons with established suppurative lesions of the brain or lungs showed little response to treatment.

Therapeutic value in ophthalmology

Dunnington and von Sallmann discuss the therapeutic value of penicillin in ophthalmology. A review of the literature shows that penicillin has been used with success in many cases of blepharitis and conjunctivitis and in a moderate number of cases of benign corneal ulcer and infected corneal wounds, but there is no report of its use in severe infections of the globe. The results obtained in 10 cases of severe eye infections treated with penicillin in Presbyterian Hospital, New York, and in the treatment of experimental intra ocular infection by a mannitol positive strain of *Staphylococcus aureus* in 10^{-4} dilution, of the eye in rabbits, are described. Some of the cases were of infections of metastatic nature and some of exogenous infections, such as ulcer of the cornea and postoperative or post traumatic endophthalmitis. It was concluded that infections of the lid border and conjunctiva with pyogenic cocci and gonococci could be effectively treated with penicillin, but cases of severe corneal infection and of exogenous intra-ocular infection of the same bacterial origin were too few in number to give an adequate basis for judgment of their general response to penicillin. The prognosis in such cases, however, seemed to be more favourable with penicillin treatment if the destructive process were not too advanced. The experimental results in rabbits showed that infections of the deeper portions of the lens were not benefited by penicillin iontophoresis, but were regularly checked by intra-ocular injections of a penicillin solution given 6 hours, and occasionally when given 24 hours, after inoculation. A single injection of penicillin given within 12 hours after inoculation arrested staphylococcal infection of the vitreous, but did not do so if it was given 24 hours after. Only moderate and transient inflammatory reaction was caused by penicillin injected into the anterior chamber of the rabbit's eye.

Penicillin therapy in ocular infections is described by Bellows. After intravenous injection penicillin can be demonstrated in the ocular tissues after subconjunctival injection or topical administration penicillin rapidly diffuses into the tissues and fluids of the anterior segment

of the eye in a much greater concentration than can be obtained by massive intravenous doses, but with only moderate concentration in the vitreous, uveal and retinal layers. For deep infections of the eye or retrobulbar space parenteral administration is the only available route. The author discusses local penicillin therapy in detail. As penicillin in solution often rapidly loses its potency, solutions should not be made up for longer than 24-48 hours before they are to be used. The strength of solution usually recommended is 200-500 units per cubic centimetre but Bellows in this investigation most often used a solution of 2,500 units per cubic centimetre. One drop of the solution was instilled into the conjunctival sac hourly day and night; in the less severe cases this was done during the day alone. In cases of severe corneal ulcers constant corneal baths of the solution for one hour several times daily were given. Since the application of penicillin in drops has disadvantages the author investigated experimentally the practical possibilities of ointment as a vehicle. The penetrating power of penicillin in four ointments was tested in the eyes of anaesthetized rabbits. The following is the order of suitability in which the ointments are clinically recommended: (1) grease base: simple ointment (U.S.P.); (2) oil-in-water emulsion-type base; (3) lubricating jelly. The fourth, a vanishing-type stearate base, although it had the highest penetrability, is not recommended for use because of the resultant corneal damage which was observed in the experimental animals. Local penicillin therapy was found to be effective in acute and chronic infections of the lids, conjunctivae and corneae caused by penicillin-sensitive organisms. In one case of chronic staphylococcal conjunctivitis of 15 years' duration cure was obtained in 3 weeks. Two cases of chronic exudative choroiditis and one gonococcal iridocyclitis were not improved by local and parenteral penicillin therapy. Bellows also reports on 4 cases in which local ocular penicillin therapy produced a true hypersensitization reaction.

Mietus describes the use of penicillin in 4 cases of severe ophthalmic disorders. The penicillin used was freshly prepared and of known potency. (1) The first case was of injury to both eyes; there was a traumatic rupture of the left eyeball, which was subsequently enucleated, and the right eye was endangered by corneal laceration, traumatic cataract and severe scleral laceration. All efforts were devoted to saving this eye. Two drops of a solution of penicillin, 250 units per cubic centimetre, in isotonic sodium chloride were instilled into the right eye twice hourly day and night for 21 days. The eye settled down and Mietus believes that the use of penicillin prevented the spread of infection through the scleral laceration. (2) In the second case penicillin solution instillations were made in both eyes, with excellent results. The eyes showed congestion and minute corneal ulcers; smears and cultures showed infection by non-haemolytic *Staphylococcus aureus*. (3) In the third case injection of 0.25 cubic centimetre of penicillin solution was made into the anterior chamber of an eye which had suffered a perforating injury and on which iridectomy had been performed; there was much congestion and many corneal deposits. The penicillin was instilled after paracentesis had been carried out with a sharp No. 23-gauge needle and an equivalent quantity of aqueous humour had been removed. The eye became white in 24 hours, but unfortunately clearing of the anterior chamber disclosed a massive retinal detachment. (4) The last case was one of a perforating injury, with entrance and exit wounds, from a gun pellet. The eye showed marked ciliary congestion and became very injected and painful and some oedema of the lid developed. Penicillin solution was injected into the anterior chamber by the same technique as that described above but the quantity of solution instilled and of aqueous humour withdrawn was 0.5 cubic centimetre. The patient was also given 25,000 units of penicillin systemically 3-hourly day and night for 42 days. The eye settled down and the author believes that it was saved by the use of penicillin. He concludes that the method of injection of penicillin into the anterior chamber, since it appears to offer therapeutic promise, deserves further investigation.

In venereal diseases

In addresses given by Fleming¹ and Suchet to the Medical Society for the Study of Venereal Diseases, Fleming describes the nature and bacteriostatic effects of penicillin. Penicillin can be administered either in the form of its sodium or its calcium salt, both by systemic injection and locally. Routine treatment of venereal disease with penicillin is not allowed, but a few cases of gonorrhoea have received experimental treatment with doses of varying strengths. The number treated was not sufficient to decide the best method of dosage, but nearly all were cured after one, two or three injections. Fleming commented on one case of syphilitic chancre with positive Wassermann and Kahn reactions, which was treated with 1,200,000 units of penicillin over a 10-day period. The chancre healed and the Wassermann reaction became negative and has remained so for several months. Suchet discusses his impressions of the treatment of 70 cases of venereal disease with penicillin. For acute gonorrhoea in males 100,000-120,000 units appear to be needed, better results being obtained by splitting the total dosage into several injections. The gonococci in these cases disappeared within 4½ hours of injection; the discharge became more profuse at first, but cleared up later. Four women with gonorrhoea and 4 cases of gonococcal arthritis also did well on the treatment. Suchet described two cases of syphilis which were treated, the first being that of a primary chancre in which the Wassermann and Kahn reactions were negative a month after treatment and have remained so ever since. The second was a case of tabes dorsalis with a perforating ulcer of the foot. Increasing intrathecal injections of penicillin were given over a 10-day period until a concentration of 2,000 units per cubic centimetre produced meningeal symptoms. The ulcer finally healed after local application of penicillin. Suchet thinks that gonorrhoea probably can

always be cured by administration of penicillin, but the value of the substance in the treatment of syphilis has not yet been sufficiently tested

Penicillin failures

Bloomfield, Kirby and Armstrong discuss "penicillin failures" in a series of over 100 patients treated with that drug. In this series 7 deaths occurred, 2 of which only could be attributed to failure of penicillin therapy. The first of these was a case of *Staphylococcus aureus* bacteraemia in a woman with an old rheumatic heart disease in which, in spite of intensive penicillin therapy, death from toxæmia resulted. The second death occurred in a case of recurrent *Staph. aureus* sepsis thought to be due to insufficient penicillin administration. The authors give clinical examples to support their opinion that failure may occur when either the total amount of penicillin or the length of treatment given is inadequate. In certain cases in which closed collections of pus are present—as in osteomyelitis or empyæmia—penicillin alone may not be sufficient to effect a cure without resort to surgical interference, even when the invading organism is highly penicillin-sensitive *in vitro*. Bloomfield, Kirby and Armstrong describe a case of acute streptococcal septicaemia after burns, in which glomerular nephritis developed during the course of the illness. Intensive penicillin therapy cleared up the septicaemia but the nephritis remained unchecked, and the authors believe that penicillin is of no use in the treatment of glomerular nephritis. Poor results were obtained in the treatment of 3 cases of pneumococcal meningitis and although no definite conclusions can be drawn from so small a series, it seems likely that penicillin should be combined with sulphonamides to give the best results. In 10 cases of non haemolytic streptococcal subacute bacterial endocarditis two strains were found to be penicillin resistant *in vitro* and this factor might be a potent cause of failure of penicillin therapy. Finally there are certain diseases, such as lymphoid leukaemia, mycosis fungoides and chronic rheumatoid arthritis, in which penicillin is of no use at all in effecting a cure.

Sulphapyrazine

Effects on children

Vandegrift studies the therapeutic effects and the toxicity of sulphapyrazine in moderate and in severe infections in 119 unselected children in hospital. The dose for infants was 1 grain per pound of body weight per 24 hours, the initial dose was half the total and the other half was divided into six 4-hourly doses. Children over 6 years of age received 2 grammes initially and 0.5 gramme every 4 hours. The maximum drug concentration in the blood was reached in 4 hours, the 24-hour blood level of all patients being lower with sulphapyrazine than it was with other sulphonamides. The drug diffuses into the spinal fluid reaching a level of 50–60 per cent of the blood level. Sulphapyrazine is slowly absorbed from the intestinal tract and increasing the dose did not accelerate the rate of absorption, the low blood level attained was, however, therapeutically effective. In very ill patients sodium sulphapyrazine was given intravenously for 24 hours and orally afterwards. There is danger of renal damage from initial high blood level, especially in young infants. Those unable to retain the compound by mouth were treated first by subcutaneous injection of 0.5 per cent solution ($\frac{1}{4}$ grain per pound of body weight every 8 hours) in physiological saline for 24–48 hours and afterwards were given sulphapyrazine orally. In acutely ill children the subcutaneous is better than the intravenous route. Untoward symptoms were few. No rise of temperature, no nausea and no vomiting were attributable to the drug. There were one case of gross haematuria and 9 cases of microscopic haematuria. Blood cells were not affected and no toxic results were recorded. There was no evidence of sensitivity to the drug.

Testosterone propionate

Effect on bladder tone

Mueller and Hamilton made cystometric studies for the purpose of testing the effect of testosterone propionate on bladder tone. Six men with benign prostatic hypertrophy and 2 women complaining of frequency of micturition and stress incontinence without infection, each had one cystometrogram taken and then received intramuscular injections of 25 milligrams of testosterone thrice weekly. A second cystometrogram was obtained from each patient after 2–7 weeks of androgenic treatment. After testosterone medication intravesical pressures which were recorded after introduction of increasing amounts of fluid into the bladder were higher in all the men and in one woman as were those pressures which developed both before discomfort was first noted and before pain became intolerable. The volumes of fluid held by the bladder at the first appearance of pain and at the onset of severe pain were similar to or slightly smaller than those found in the first cystometrograms. In most instances the intravesical pressure at which desire to micturate was first experienced was increased, but the urinary volume at this point did not vary uniformly. Intermittent rectal palpation during treatment revealed no change in prostatic size or consistency which could explain the improved control of micturition experienced by most patients. Improvement tended to lapse on cessation of medication. The authors consider that the increased intravesical pressure accompanying androgenic treatment can be attributed to augmented tone of the bladder musculature and that this increased tone was much in excess of the normal range of variability and could not be accounted for by the instrumentation incidental to cystometry.

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TOXICOLOGY: HOMICIDAL, SUICIDAL, AND ACCIDENTAL POISONING

See also B.E.M.P., Vol. XII, p. 59; and Cumulative Supplement, Key Nos. 1491-1527.

Gases

Carbon monoxide

Polycythaemia.—Brieger reports on experimental findings in dogs and men which provide some new information on carbon monoxide polycythaemia. In acute carbon monoxide poisoning an initial increase of haemoglobin and erythrocytes in the circulating blood, attributed

to early splenic contraction, was not noted in the series. Significant polycythaemia was a late effect of strong blood saturation with carbon monoxide and reached its full development only several days after exposure. In one dog permanent polycythaemia developed, another showed a moderate increase of haemoglobin and erythrocytes, characterized by reticulocytosis and appearance of normoblasts, and another showed a significant decrease of haemoglobin and erythrocytes. Thus onset, development and degree of polycythaemia varied considerably in individual dogs. No significant correlation coefficient between haemoglobin and erythrocyte changes was noted. Six dogs were exposed for 11 weeks to an air concentration of 0.0096 volume per cent resulting in an average blood saturation of 0.1 per cent carbon monoxide. The erythrocytes showed a significant increase after 3 weeks, reaching a maximum at 9 weeks, the greatest increase was 43.75 per cent. Haemoglobin values reached their maximum after 6 weeks, the greatest increase being 45 per cent. After 9 weeks erythrocytes and haemoglobin fell respectively to and slightly below the original level. In several dogs, haemoglobin again increased in the 3 months after termination of the exposure, one dog showing a trend towards permanent polycythaemia. Since significant erythrocytosis occurred only late, it could not prevent the noxious effects on the circulatory and nervous systems in either acute or chronic carbon monoxide poisoning.

Hydrocarbons

Kerosene

Fatal poisoning in a child—Deichmann and his colleagues describe a case of acute kerosene (paraffin) poisoning in a child aged one year. The child drank a mouthful of the poison and coughing ensued immediately. Cyanosis and collapse occurred within 50 minutes in spite of gastric lavage with a solution of sodium bicarbonate. Two hours after admission to hospital the pulse rate was 136, the respiratory rate had risen to 80 and the temperature was 102.2° F. There was impaired resonance over the entire thorax and many coarse rales and rhonchi were heard on auscultation. Death took place 9 hours after ingestion of the kerosene. Necropsy showed the presence of acute pulmonary congestion and oedema, acute diffuse confluent lobular pneumonia, acute bronchitis and bronchial lymphadenitis. Other findings included slight toxic nephrosis and fatty infiltration of the liver, mucosal erosions of the colon and passive congestion of the abdominal viscera. It is considered that the pulmonary changes in kerosene poisoning are produced by aspiration of the poison into the respiratory tract and by absorption from the gastro intestinal tract with subsequent excretion into the lungs. This view is supported by experiments on animals in which the pathological changes in the lungs were of the same general character whether administration of kerosene was by stomach tube or by intraperitoneal injection. The lethal oral dose for adult guinea-pigs and rabbits varied from 20 to 28 millilitres per kilogram of body weight. By intravenous injection the lethal dose for rabbits was 0.18 millilitre per kilogram and, by the intraperitoneal route, 6.6 millilitres per kilogram. Young rats were found to be more susceptible to the poison than were adult animals. This finding should be correlated with the fact that, although numerous fatalities have occurred in children, no fatal cases have resulted in adults despite reports of the ingestion of considerable quantities of kerosene.

Brieger, H. (1944) *J. industr. Hyg.*, 26, 321.

Deichmann, W. B., Kitzmiller, K. V., Witherup, S., and Johansmann, R. (1944) *Ann. intern. Med.*, 21, 803.

TRACHOMA

See also B. E. M. P., Vol. XII, p. 209, and Cumulative Supplement, Key No. 1545.

Epidemiology

Trachoma in London

Elimination of the disease—Sorsby¹ traces the history of trachoma in London schoolchildren. He relates how widespread was the disease in children under the Poor Law authorities in the early nineteenth century. In 1903 the White Oak (London County Council) Hospital was opened, and a year later Highwood Hospital, for the treatment of trachoma. Since then admissions for trachoma fell steadily from 292 in 1903 to 7 in 1943. In 1918 it was possible to close Highwood and in May 1944 the remaining 5 trachoma cases were discharged from White Oak Hospital and the trachoma block was closed. Trachoma has not however disappeared from the adult population of London and in each case the patient is a potential source of infection to others. In Glasgow trachoma has been notifiable since 1914 with provision of out-patient and in-patient treatment. Notifications have fallen from 112 in 1915 to 3 in 1943. Sorsby concludes that the experience of White Oak Hospital which shows how trachoma may be eliminated from a heavily infected child population and at Glasgow where adults demonstrate that notification of trachoma cases in London with provision of treatment centres are the logical steps to take in order to eliminate the residual problem of trachoma in London.

Incidence and geographical distribution

Trachoma in West African negroes—Trachoma in West African negroes is discussed by Scott, who states that it is only recently that the prevalence of trachoma amongst them has been recognized. In this series pannus was considered to be the most important point in the

diagnosis. When subepithelial infiltration or scarring was present with pannus, trachoma was diagnosed. When pannus only was present the case was classified as one of doubtful trachoma. Scott found that approximately 5 per cent of schoolchildren, 10 per cent of soldiers and 25 per cent of the population in some villages in the Gambia were infected. Ten per cent of Gold Coast and Nigerian soldiers and 2 per cent of Cameroon soldiers showed infection. One-third of the number of cases showing only either pannus or vessels resulting from cleared pannus, were diagnosed as of doubtful trachoma. Discussing the possible differential diagnoses in these Scott states that it is difficult to exclude the possibility of syphilis in a community infected with yaws, but that in many of the doubtful cases the Kahn test was negative. A vitamin deficiency does not appear to be a causative factor. The author describes the results of an examination of 300 cases based on a classification into the four stages described by McCallan. No seasonal incidence of trachoma was found. Scott describes 2 cases in which the first stage of trachoma was noted in infants 8 and 12 months of age, who were subsequently seen with complete regression. One monocular case was seen. Inclusion bodies were seen in 13 of 30 conjunctival scrapings. Scott states that the cases discovered on routine examination were untreated and when seen later were mostly unchanged, some had improved and a very few were worse. He concludes that, as the complications of the disease as seen are so mild, and as it tends to settle down on its own, treatment should be directed towards hygienic and other measures for the prevention of spread and towards the treatment of secondary infections when these occur.

Treatment

Treatment of conjunctiva

Importance of sulphonamides.—Sorsby,² from his experience in treating some 200 patients over a 10-year period, concludes that considerable departures from the classical measures are now suitable in treating trachoma. The use of the traditional copper sulphate stick is especially condemned. During the stage of follicles and sodden fornices, full doses of sulphonamides should be administered, the follicles should be expressed and the palpebral conjunctiva should then be painted with saturated solution of quinine bisulphate thrice daily for 7–14 days. Painting with 30 per cent sodium sulphacetamide solution has recently been found to be equally effective. These procedures will usually convert this stage into that of trachomatous chronic conjunctivitis with a relatively featureless but characteristic moist appearance. At this stage any application of copper must be rigorously avoided. Painting of the lids twice daily with 0.5–2 per cent mercuric chloride in glycerin will usually render the eye dry within 6 months. More recently, better results have been obtained by painting the lids once daily with 30 per cent sodium sulphacetamide solution and the application thrice daily of 6 per cent sodium sulphacetamide ointment. Corneal massage with a small glass rod should be done once daily. In the stage of healing trachoma, with a dry eye, sodium sulphacetamide ointment can be applied twice daily until complete clinical cure is obtained. Alternatively, zinc sulphate drops, 0.25 per cent, or, less desirably, copper sulphate drops, 0.25 per cent, can be used thrice daily. A number of cases of trachoma have been rendered non-infectious within 3 months and have been clinically cured in 6 months, mainly by local sulphonamide therapy, the only adjuvants being one or more courses of general sulphonamide therapy and one or more expressions. These facts, Sorsby concludes, strongly suggest that the sulphonamides are specific against the virus of trachoma and not merely against any associated secondary infection.

Scott, J. G. (1945) *Brit. J. Ophthalm.*, 29, 244.

Sorsby, A. (1944)¹ *Brit. med. J.*, 2, 220.

— (1945)² *Brit. J. Ophthalm.*, 29, 98.

of the chair produced illusions of spatial orientation. The disturbances were relatively independent of the vegetative reactions of motion sickness. The observation that nystagmus occurred after rotation suggests that symptoms of motion sickness may be elicited not only by stimulation of the maculae but also by stimuli acting on the ampullary crest. The absence of nystagmus in seasickness is ascribed to incomplete rotations causing stimuli which are unable to elicit vestibulo-ocular reflexes.

Spiegel, E. A., Oppenheimer, M. J., Henny, G. C., and Wycis, H. T. (1944)
Har Med, 6, 283

TRYPANOSOMIASIS

See also B E M P, Vol XII, p 263, and Cumulative Supplement, Key No 1553

Treatment

Curative

Pentamidine—Saunders, Holden and Hughes report on further observations on the treatment of trypanosomiasis with Pentamidine. Clinical and cerebrospinal fluid findings as regards cells and globulin, and results of treatment in 50 cases are tabulated. Of these, 7 were old cases, followed up for periods of up to 3 years. Twelve later cases are reported on in detail, with emphasis on the immediately observed effects of Pentamidine administration. More recently treated cases make up the total. In the authors' experience, the only serious immediate effect was a fall of blood pressure, which in one case was sufficient to cause fainting. Injection of atropine, but not ephedrine, prevented the fall of pressure, which was, however, trivial when the injection was given very slowly. Dosage commenced with 0.5 milligram per kilo of body weight and increased, usually by 0.02 milligram daily, to 2 milligrams per kilo. Probably with very slow injection quicker increases would be safe and might give better final results such as occurred in one patient who was given abruptly increasing doses. Saunders, Holden and Hughes have not yet observed a case in which peripheral trypanosomes persisted or reappeared even on clinical relapse. Of 8 cases with a cerebrospinal fluid cell count of under 30, all patients had immediate apparent cure, but one relapsed. Of 16 cases with a cell count of over 30 or showing advanced symptoms, 3 patients in whom the disease was very advanced and 7 in whom it was moderately advanced received little or no benefit; in 6 there was a good immediate result, but 4 relapsed within 2 years; 2 patients, each with a cell count of over 600, have remained well for more than 2 years.

Saunders, G. F. T., Holden, J. R., and Hughes, M. H. (1944) *Ann Trop Med Parasit*, 38, 159

TUBERCULOSIS

See also B E M P, Vol XII, p 286, and Cumulative Supplement, Key No 1554

Aetiology and bacteriology

The tubercle bacillus

Bactericidal action of *Aspergillus fumigatus* strains—Asheshov and Strelitz investigate a report that culture filtrates of a strain of *Aspergillus fumigatus* show antibiotic activity against *Mycobacterium tuberculosis*. So far no substance active in a pure or even crude form against the tubercle bacillus has been described. The mould grown at room temperature produces substances active against Gram positive cocci, Gram negative bacilli and some acid-fast bacilli. It is believed that there are 2 different substances, not yet separated, one active against Gram positive cocci the other against Gram negative bacilli. The one active against Gram positive cocci is also active against *Mycobacterium tuberculosis*. Both substances are obtained in crude form from the medium by various extractives. At present efforts are directed to the purification of the active substances. The activity of partially purified preparations is already established by various tests indicating that the preparations possess a large amount of bacteriostatic activity against *Staphylococcus aureus* and against the Calmette Guérin strain of *Mycobacterium tuberculosis*, and that their bactericidal activity against the bacillus is equal to or slightly lower than their antistaphylococcal activity. No bactericidal action has been observed on the avian type of *Mycobacterium tuberculosis*. The authors have postponed animal experiments on the toxicity and activity of the crude preparations until these can be obtained in much purer forms.

Epidemiology

The Prophit Survey

Daniels analyses the findings of the Prophit Survey, from January 1935 to April 1943, on primary tuberculous infection in nurses. During this period 3,764 nurses entered the Survey. Each gave details of past health, contacts and occupation. An initial Mantoux test was made and an x ray film of the chest was taken. These tests were repeated annually and any illness since the previous tests was recorded. The nurses came from two groups of hospitals, the first admitted all types of patients including cases of tuberculosis, the second rarely accepted chronic cases and only one had a tuberculous ward. Of the 3,764 subjects, 50.3 per cent were positive to old tuberculin 1 in 10,000 or 1 in 100,000, 30.5 per cent were positive to 1 in 1,000, 19.2 per cent were negative. The rate of Mantoux conversion in the first year was 78.3 per cent and 58.4 per cent in the hospital groups respectively. This difference is probably associated with increased exposure in the first group. Amongst those nurses whose initial chest x ray was clear, 33 cases of tuberculosis occurred in 452 initially Mantoux negative, 43 cases in 2,120 initially Mantoux positive. Cases of tuberculosis are defined as recommended by the

Prophit Committee. In the 33 cases initially Mantoux negative a wide diversity of types of tubercular lesion was seen. The higher the sensitivity shown at the first positive Mantoux test after conversion the greater was the subsequent incidence of tuberculosis. The annual case rate was 7.4 per 1,000 in nurses initially Mantoux positive, 18.8 per 1,000 in those initially negative. Two nurses in the Survey died of tuberculosis. The incidence of tuberculous morbidity is higher in nurses initially Mantoux negative than it is in those initially positive and is particularly high during the year following conversion. Acquired immunity is partly responsible for the lower rate in the Mantoux positive nurses; this group can be regarded as one in which the susceptibles have been eliminated. Individual resistance to tuberculosis is lowest between the ages of 15 and 30 years. This interim report shows that primary tuberculous infection in young women is not essentially benign and that the risk of development of tuberculosis after primary infection in young adults is serious. It is recommended that a controlled method of antituberculosis vaccination be employed. Cases of known open tuberculosis should be admitted to special wards where tuberculin negative nurses should not work. Those nurses should be retested every 3 months until they are tuberculin positive and those known to be recently infected should have frequent and careful medical supervision.

Immunity and allergy

Hypersensitivity

Passive transfer by the blood.—Corper and Cohn state that three biological phenomena of importance, which have been demonstrated in tuberculosis, are (1) specific tuberculo-immunity, (2) specific tuberculo-bacillary allergy and (3) specific tuberculin allergy. A fourth phenomenon, specific tuberculin anaphylactic hypersensitiveness, has been shown in experiments with guineapigs to be transferred to offspring born more than a year after the sensitization of the mother, and it can be passively transferred by means of the blood in about 45 per cent of donors. Specific tuberculin anaphylactic hypersensitiveness is not produced by tubercle bacilli or by tuberculosis. The first 3 phenomena are not passed from mother guineapigs to their offspring. The authors describe experimental results demonstrating that specific tuberculosis immunity and tuberculin allergin hypersensitiveness are not passively transferable in guineapigs. Specifically immune and allergically hypersensitive guineapigs were bled to the amount of 12 cubic centimetres 1 and 2 months after vaccination. The tabulated results transferred to normal guineapigs. A control group was included. The tabulated results showed that the specific immune donor animals had a marked protection against subcutaneous infection with virulent human tubercle bacilli, and that this protection was not transferred passively to the recipient guineapigs by the injected citrated whole blood from the donors. The same result was noticed with regard to tuberculin allergic hypersensitiveness.

Prognosis

Leucocyte counts

Lymphocytosis in a children's sanatorium.—Finucane and Philips report on an epidemic condition occurring in a tuberculosis sanatorium in the District of Columbia in which in 21 children, from 1½ to 5½ years of age, there developed a marked total leucocytosis with a relatively big proportion of lymphocytes and without clinical signs or symptoms. A similar condition had been reported only 4 times previously, one writer describing his 2 cases as those of "infectious lymphocytosis". Another report varied only in that the child had acute abdominal symptoms, headache and fever. Pronounced lymphocytosis occurs in pertussis and lymphatic leukaemia, moderate lymphocytosis in infective mononucleosis and slight lymphocytosis in tuberculosis and post-infective conditions. The first of the 21 cases now reported on was discovered through a routine 6-monthly blood examination. In May the count showed leucocytes 10,000 with 80 per cent lymphocytes. Five days later the leucocyte count was 73,100 with 91 per cent lymphocytes. Five days later still the leucocytes were 87,400 with 93 per cent lymphocytes. Lymphocytes and 8 days later still the leucocytes were 87,400 with 93 per cent lymphocytes. Erythroblasts seemed to be normal in appearance. On the same day of the first patient's maximum count the second case was discovered. The Paul-Bunnell test was negative in both. As both cases were considered to be infectious, leucocyte and differential counts were made in all the children (approximately 100); 18 further cases were found, the twenty-first being discovered by routine blood examination on admission to the Sanatorium of a child from Washington. Some of the children had severe, and an equal number had slight, tuberculous infection. In cases in which there was no such infection before, enlargement of glands or spleen did not develop. The condition lasted from 2½ to 7 weeks, the average being about 4½ weeks. No infective agent was discovered.

General review

Puffer, Stewart and Gass state that studies in the prognosis of tuberculosis are usually based on data obtained from sanatoria and include in consequence a large proportion of advanced cases. Owing to the discovery by miniature radiography of the future outlook in such cases, latent disease there is need for a more exact knowledge of the future outlook in such cases. The authors discuss a series of 913 cases in Williamson County, Tennessee, diagnosed over a period of 12 years as being reinfection type tuberculosis. Of these cases 384 were considered to be active on diagnosis and 39 per cent were classified as minimal. A further 268 were classified as arrested and 261 with x-ray demonstrable lesions, but without physical signs, were classified as latent apical cases. Comparing observed and expected death rates, only 2 clinical

groups of the whole series the far advanced and the moderately advanced cases, showed a larger death rate than could normally have been expected, the increase being 16 and 41 times as great respectively. Division into sexes showed that young females with advanced disease did not do as well as did males. The authors state that there is a considerable incidence of mortality in young adults who are found only when the disease has reached an advanced state. After analysis of the series regarding changes in the status of the disease during observation, the authors conclude that the prognosis is unfavourable for young adults with moderate or far advanced disease. Patients under 45 years of age with minimal, minimal arrested and latent apical tuberculosis do not do as well as do similar cases over that age. Males in the young age group retrogress more often than do females. Of 455 tuberculosis patients under 45 years 289 are recorded as having a sister, brother or parents known to have had tuberculosis and analysis suggests that in cases without a family history a less serious form of the disease tends to develop. The course of the disease in the minimal, minimal arrested and latent apical groups with family histories seems to be less favourable than it is in those with no known family contact. Household contact during observation does not appear to be an adverse factor. The authors conclude, however, that further data are necessary for the evaluation of the above factors.

Diagnosis

Detection of tubercle bacilli

Examination of gastric contents for tuberculosis—Feld discusses the significance of tubercle bacilli found on examination of gastric contents, a routine procedure since 1933 in examination of children at Murdale Sanatorium, Wisconsin and now extended in the case of adults for diagnostic and treatment purposes and for estimating freedom from active infection. The procedure is especially useful in patients who have no sputum or whose sputum is negative. The undiluted gastric contents are aspirated from the fasting patient. All specimens are cultured on three slants of Petragnani's medium. Reliance cannot be placed on the detection of tubercle bacilli in concentrated smears. Patients negative for sputum but positive for gastric contents are likely to have positive sputum subsequently. In the absence of the gastric examination many cases would be discharged from sanatoria while they were still actively infective. Five consecutive negative examinations of gastric contents qualify a patient for discharge. During a period of 5 years, 868 adults had a total of 4,204 examinations of gastric contents. Of these, 404 had negative gastric contents after 1,338 examinations. The remaining 464 had 2,866 examinations of which 1,271 were positive. Each of these two groups was divided into (1) no sputum, (2) negative sputum and (3) positive sputum subgroups. In order to save time sputum cultures and gastric examinations were carried out simultaneously. All positive sputum cases were found to be gastric positive if the examination had been repeated up to 5 times. On the other hand, if the sputum were negative and the gastric contents were also negative after 5 consecutive examinations, there was not any evidence of active pulmonary tuberculosis.

Prevention

Sanatorium treatment

Control of spread of wartime tuberculosis—At the fortieth annual meeting of the American National Tuberculosis Association at Chicago, Kraabel outlined a scheme to combat the considerable increase in tuberculosis caused by the recent war. It has been found that 40 per cent of the war veterans suffering from tuberculosis left hospital against medical advice, or absented themselves without leave, and went home, to the danger of their families and neighbours. In order to counteract the tendency, the efforts made by the medical profession, tuberculosis associations, public health authorities and volunteer groups must be coordinated and increased. The American Legion with 1,300,000 members and its Auxiliary with 600,000 members are concentrating on education of tuberculous war veterans and their families in the urgent necessity of patients remaining under hospital care and treatment until arrest or cure of the disease. Service officers visit the patients in the wards, persuade them to comply with medical instructions and reassure them about the condition of their relatives at home. It had been found that many patients left hospital against advice because of homesickness or of anxiety, financial or otherwise, about their families. The families are visited by female Auxiliary workers and are instructed concerning the danger to all around him of a patient with active tuberculosis. Public health authorities and Legion service officers should be notified of men leaving hospital against advice, and methods of controlling such men should be decided upon. It has been suggested that since many of the tuberculous men are pensioned funds might be withheld as a disciplinary measure, but amended legislation would be required before such a step could be taken.

Asheshov, I. N., and Strelitz, Frieda (1944) *Science*, 101, 119

Corper, H. J., and Cohn, M. L. (1945) *Amer Rev Tuberc*, 51, 312

Daniels, M. (1944) *Lancet* 2, 165, 201, 244

Feld, D. D. (1944) *Amer Rev Tuberc*, 50, 481

Finucane, D. L., and Philips, R. S. (1944) *Amer J Dis Child*, 68, 301.

Kraabel, T. O. (1944) *Amer Rev Tuberc*, 50, 391

Puffer, Ruth R., Stewart, H. C., and Gass, R. S. (1945) *Amer Rev Tuberc*, 51,

TUBERCULOSIS, GENERALIZED

See also B.E.M.P., Vol. XII, p. 298.

Clinical picture and treatment

Acute generalized massive tuberculosis

Effect of streptomycin on guineapigs.—Feldman and Hinshaw describe the effect on experimental tuberculosis in guineapigs of administration of streptomycin, an antibiotic substance which has been shown to be capable of marked *in vitro* bacteriostatic and bactericidal effects on a human strain of *Mycobacterium tuberculosis*. Twelve male guineapigs, weighing approximately 500 grammes each, were inoculated subcutaneously in the sternal region with 0.1 milligram of a 16-day-old culture of tubercle bacilli. Four of the animals were treated: administration of streptomycin was started in 2 subjects immediately after infection and in the other 2 after an interval of 2 weeks. The daily dose was 75 milligrams (2,775 units) given subcutaneously, 5 times daily at 3-hour intervals, except in the case of one of the two animals in which treatment with half that dose was started immediately after infection. Visceral tuberculosis was minimal in the treated animals; in each of the controls the disease was grossly evident and microscopically the destructiveness of the advancing tuberculous process was much greater than that in the treated animals. Toxicity was absent, and there were no recognizable tissue changes in the kidneys, suprarenal glands, liver, lungs, urinary bladder, lymphatic glands or bone marrow of the treated animals. In the second investigation there were 10 controls and 10 animals treated with 3,500 units, divided into 4 daily doses at 6-hour intervals, for a week; the amount was then reduced to 1,750 units daily—some animals had lost weight—for 19 days when on receipt of a better purified preparation of streptomycin, the dose was increased to 3,000 units daily for 15 days and subsequently to 6,000 units for 20 days. Results were comparable to those of the first experiment and microscopical examination revealed no toxic effects in parenchymal organs.

Chronic generalized massive tuberculosis

Involvement of female generative system.—Haas presents a series of 62 cases of genital tuberculosis in females who were seen between 1920 and 1941. The diagnosis was confirmed by histological examination in all cases. No pathognomonic signs or symptoms were found, and existence of abdominal pain and fistulae or sinuses was the commonest reason for admission to hospital. Menstrual disturbances were present in 58.1 per cent of cases; irregularity and menorrhagia were more common than was amenorrhoea. Forty-eight per cent of the patients in the series were found to have active tuberculosis elsewhere—in the lungs in 40.3 per cent—but the author points out that a more thorough search might result in a greater incidence being found. Eight patients had conservative treatment, of whom 4 who were in an advanced state of generalized tuberculosis died; of 3 who were treated on general lines 2 are alive and well after respectively 10 and 9 years. Fifty-four patients were treated surgically; of these 49 had laparotomies—13 had a complete pelvic exenteration; in 13 the cervix was not removed and the remaining 23 had a variety of surgical treatment. The incidence of wound infections or fistulae was smallest in the first group. In discussing the distribution of the tuberculosis, the incidence of involvement of cervix was 27.7 per cent in the 18 cases in which the complete genitalia were available for examination. Haas advises that whenever possible all the genitalia, including the cervix, should be removed if operative treatment is indicated. It was not possible to compare the results of surgical and conservative treatment in this series owing to differences in the severity of the disease in the two groups. Of the whole series 45 patients are now alive and of these, over half the number claim to be in good health.

Feldman, W. H., and Hinshaw, H. C. (1944) *Proc. Mayo Clin.*, 19, 593.

Haas R. I. (1944) *Amer. J. Obstet. Gynec.*, 48, 69.

patients recovered. These cases emphasize the importance of the tick as a cause of human tularaemia. Prophylactic measures suggested include avoidance by the Army of tick-infested areas and daily thorough inspections for the presence of ticks. These should be removed with the bare fingers, without being crushed, since the infectious agent can penetrate the unbroken skin.

Treatment

Streptomycin

Experiments on mice—Heilman presents the results of studies undertaken for the purpose of determining the effectiveness of the antibiotic agent streptomycin in the treatment of experimental tularaemia. *Pasteurella tularensis* proved to be very sensitive *in vitro* to the action of streptomycin. Experiments then showed the susceptibility of mice to infection with virulent strains of *P. tularensis*. Of 30 infected untreated mice, all died of tularaemia within 96 hours after inoculation. Thirty mice which each received 1,000 units of streptomycin daily for 10 days all survived. Of 12 mice which each received only 500 units of streptomycin daily, 5 only survived. Of 6 treated mice from the group originally inoculated with 10 times the lethal dose of the organism, none harboured the organism in the spleen when examined 27 days afterwards. Treated mice from this group were found to have but slight immunity to 1,000 times the lethal dose when tested 28 days after the original inoculation. Treated mice from the group which received an initial inoculum of 100 times the lethal dose of the organism showed considerable immunity to 100 times the lethal dose when tested 23 days after the original inoculation. The protective action of streptomycin on experimental tularaemia suggests that the drug may be useful in the treatment of such infections in man, in whom the mortality rate is reported to be 3-5 per cent and the morbidity rate high. Although, in treatment of this widespread disease, serum is reported to be of value in reducing both mortality and morbidity, it often causes sickness.

Byfield, G. V., Breslow, L., Cross, R. R., Jun, and Hershey, N. J. (1945)

J. Amer. med. Ass., 127, 191

Heilman, F. R. (1944) *Proc. Mayo Clin.*, 19, 553

TUMOURS

See also B. E. M. P., Vol. XII, p. 313

Aetiology

Influence of tar and other products

Friedewald and Rous describe experiments made in order to distinguish between the initiating and the promoting elements in tumour production and to analyse the effects of tar, 1-2-benzpyrene and methylcholanthrene on the benign tumours they cause in rabbit's skin. These substances were painted on the inner expanse of the ears of adult rabbits. The effect of wound healing was ascertained by punching holes in the ears with cork borers. Detailed records were kept over long periods. The solutions used were benzpyrene in benzene and in mineral oil, benzene and methylcholanthrene in benzene, in mineral oil and in ether and tar. Benzpyrene has an effective initiating action and causes neoplastic changes much more quickly than had been held to be possible, but there was a long interval before visible growths appeared, due to its slight promoting effect. Methylcholanthrene and tar have a much stronger promoting effect, but tumours due to methylcholanthrene appear months after those produced by tar. More tumour cells are present than those which give rise to visible growths. The initiating action of benzpyrene is as effective in mineral oil as it is in benzene, but the effect of the mineral oil is to delay the formation of tumours for months after the benzene solution has produced them. Further similar experiments were carried out with tar and the polycyclic hydrocarbons in order to show how far such substances determine the character of the neoplasms they induce. Tar, benzpyrene and methylcholanthrene acting on the stratum germinativum of rabbit epidermis all produce the same types of benign tumours, namely frill horns, papillomas and carcinomatoids. The tar tumours tend to be fleshy and vigorous with considerable stroma, whereas in the case of the other agents the tumours are dry and indolent with scanty stroma, and some of the cells of the frill horns undergo a dyskeratotic change causing deeply staining bulletlike elements. Carcinomatoids occur more often with tar, as would be expected because of its pronounced promoting effect. Tar, as compared with the polycyclic hydrocarbons, causes relatively few frill horns. These agents cause a notable increase in the number of sebaceous glands with now and again resultant sebaceous adenomata. Tar does away with the sebaceous glands at an early period and therefore does not cause sebaceous adenomata. All these agents are seen not only to be able to induce neoplastic change and to promote or suppress tumour growth, but also to have considerable ability in conditioning the kind of tumour which will arise, and its structure.

Clinical features of benign and malignant tumours

Characters of malignant tumour

Secondary carcinoma of the oesophagus—Out of 599 consecutive cases of cancer in which necropsy was performed, Torson collected 19 examples of secondary carcinoma of the oesophagus. These, together with 7 similar cases, he analyses and describes. Of the 26 metastasizing tumours 24 were carcinomata, one a lymphosarcoma and one probably a melanoma. The primary tumours were in the trachea or bronchus in 8 cases, in the pancreas in 2, in the

stomach in 7, in the larynx in 4, in the breast in 2, in the testis in 1, in the mediastinal lymphatic glands in 1, and on an undetermined site in 1 case. In 8 cases the primary tumour was distant. Quoting Gross and Freedman's figures—which included examples of oesophageal tumours secondary to primary growths in stomach, breast, larynx, pancreas, testis, eye, tongue, bronchus, mediastinal lymphatic glands, prostate and tibia—the author suggests that cancer of any organ can probably metastasize in the oesophagus. In a little less than half the number of cases dysphagia was present. It was of particular interest in 3 male patients who were in the late fifties, and all under treatment for syphilitic aortitis with diffuse dilatation of the thoracic aorta. In each case there was involvement of the middle portion of the oesophagus by direct extension of primary carcinoma of the bronchus. In 2 of the 3 the presence of the primary lesion was suspected and bronchoscopic examination was performed; the third case was disclosed at necropsy. In all the 3 dysphagia had been attributed to compression of the oesophagus by the aorta.

Friedewald, W. F., and Rous, P. (1944) *J. exp. Med.*, **80**, 101, 127.

Toreson, W. E. (1944) *Arch. Path.*, **38**, 82.

TYPHUS FEVERS

See also B.E.M.P., Vol. XII, p. 325; and Cumulative Supplement, Key Nos. 1558-1560.

Fevers of the typhus group

Experimental typhus in cotton-rats

Anderson presents further observations on experimental typhus fever infection in cotton-rats, its acute course and general pathological findings being first described. Tissues of mesothelial origin were primarily involved. Depending partly upon the route of inoculation, whether intraperitoneal, intracardial or intracerebral, rickettsiae were most easily demonstrated in smears from liver and brain and from peritoneal and pericardial effusions. From these sources rickettsiae were successfully isolated by subinoculation into the yolk-sacs of eggs. Although massive doses of rickettsiae were needed to produce lethal infections in cotton-rats, their susceptibility, as measured by the development of an immunizing infection, proved to be great. With both the Wilmington murine and Breinl louse-borne strains, a lethal dose consisted of 10,000-100,000 immunizing doses. Cotton-rats proved to be more susceptible to Breinl infection than did mice. Both were equally susceptible to murine infection. Cotton-rats and guineapigs were almost equally susceptible to Breinl infection. Although infected cotton-rat liver suspensions proved to be toxic for mice, no toxic activity of rickettsial suspensions was demonstrated for cotton-rats. Three strains of rickettsiae were successfully carried in serial intracardial passage as fatal infections for cotton-rats; so far the virulence of none of these has been markedly affected by prolongation of such passage. Sublethal but infective doses of typhus rickettsiae conferred upon rats a solid immunity to reinfection with homologous virus. Cross immunity between louse-borne and murine strains was demonstrated. Sera from recovered rats demonstrably contained antitoxic, complement fixing and neutralizing antibodies, but no agglutinins for *Proteus OX 19*. Anderson describes a technique of using suspensions of infected cotton-rat livers as antigens in serum neutralization tests. Thus, neutralizing antibody was demonstrated in the convalescent sera of human beings, cotton-rats, guineapigs and rabbits. Sera tested against antigens of homologous immunological character revealed greater titres than when tested against heterologous strains.

Non-epidemic or epizootic typhus fevers

Tick typhus

Colorado tick fever.—Florio, Stewart and Mugrage state that Colorado tick fever is a mild non-fatal infection of unknown aetiology resembling dengue fever, except for the absence of a skin eruption. The evidence of transmission by the wood tick, *Dermacentor andersoni*, is circumstantial in character and the authors were unsuccessful in infecting clean wood ticks with the causative agent of the disease. Adult ticks were allowed to feed on typical cases and the progeny failed to transmit the disease to volunteers by whom they were then carried through to a new generation. The progeny failed to transmit the disease to susceptible individuals. The fever was successfully transmitted, however, to volunteers by means of injections of infective sera. The experimentally acquired disease was identical with the naturally acquired infection and successive transference did not result in any apparent change in character or virulence. The incubation period varied between 3 and 5 days, with the exception of one case in which the period was 10 days. Examination of the blood showed a decrease in the number of polymorphonuclear neutrophil leucocytes and a shift to the left. There was also a decrease in the number of lymphocytes. On the third or fourth day after clinical recovery an occasional large lymphocyte was noted containing 2-8 sharply outlined bodies in the cytoplasm. These structures have not been encountered in other diseases. Further experiments proved that an attack of Colorado tick fever confers a degree of immunity to the disease and that the fever can be transmitted to the golden hamster. The latter finding should assist in the determination of the aetiological factors. The infection is not a mild form of Rocky Mountain spotted fever since individuals immunized with ground tick vaccine against this disease are still susceptible to Colorado tick fever.

Treatment of Rocky Mountain tick typhus by intravenous methods.—According to Harrell, Venning and Wolff, intravenous injections of fluids are not harmful in the treatment of Rocky Mountain spotted fever. Successful therapy depends upon the nature of the fluids injected.

A severe form of peripheral circulatory collapse occurs in the disease and, since the osmotic pressure of the blood is not maintained at the normal level, intravenous solutions of glucose or salt rapidly leave the blood stream and may also wash proteins into the tissues. Oedema of the subcutaneous tissues and lungs can be produced by excessive administration of such injections. On the other hand, crystalloids are of value for patients with profuse sweating and diminution in the blood chlorides. Plasma and whole blood are the fluids of choice for counteracting peripheral circulatory collapse, hypoproteinaemia and oedema. Tube feeding may be necessary for patients with stupor or delirium. The diet should be rich in protein and carbohydrate in order to protect the liver and to assist in the regeneration of plasma proteins. The dietary may be supplemented by the intravenous injection of amino acids. Eradication of the infection by means of Topping's serum has been found to be effective only in the first 3 days after the rash has appeared before a sufficient number of parasites have become established in the cells. Little beneficial effect was noted in a boy who was given specific hyperimmune rabbit serum 8 days after the development of the rash. Pneumonia is a common complication of the fever, in one case the pneumonia was successfully treated by the authors with administration of sulphadiazine and application of x-rays. Lumbar punctures are recommended for the purpose of relieving severe headache. Hiccups may prove to be extremely resistant to therapy and heavy sedation may be required. Injection of procaine hydrochloride around the lumbar sympathetic ganglia may reduce the pain due to thrombophlebitis in the lower extremities.

Mite typhus

Clinical picture—Lipman and his colleagues report on 200 cases of scrub typhus in the South-west Pacific area. The infection is due to *Rickettsia nipponica*. This organism is believed to be transmitted by the larval hexapod form of the mites *Trombicula akamushi* and *Trombicula deliensis*. It is thought that the primary reservoir of infection is in ground rodents, particularly the rats and mice living in the jungle brush undergrowth and native grasses. In the cases examined by the authors the incubation period varied from 9 to 14 days. During this time one or more eschars formed at the site of inoculation. The eschars were present in 80 per cent of the patients and ranged in diameter from 1 millimetre to 1 centimetre. Each lesion was either round or oval, with a black necrotic centre surrounded by a cloudy red areola. The prodromal period lasted from 1 to 5 days. The characteristic manifestations were headache, orbital or retro-orbital pain, and regional and generalized tender enlarged lymphatic glands. The febrile stage was characterized by a high remittent fever of a diurnal type, the temperature varying between 101° F in the morning and 104° F in the afternoon or evening. The fever persisted for about 14 days and subsided by lysis. A maculopapular rash developed between the fifth and the eighth day, especially on the abdominal and anterolateral thoracic walls. There was a rise in the titre of the *Proteus* OX K agglutination reaction from 0 to 1 in 40 or higher. The cases were classified as mild, severe and cerebral. The commonest complications were pulmonary congestion, myocarditis and suppurative bronchitis. Differential diagnosis was required from other common disorders such as malaria, dengue, pneumonia and serum sickness. The mortality rate was 10 per cent. The treatment was symptomatic and convalescent serum was without benefit.

Scrub typhus—Berry, Johnson and Warshauer record their clinical observations in 195 cases of tsutsugamushi fever, with special reference to its cardiovascular effects. The pyrexial course, which usually lasted 14–21 days, subsided by lysis. The pulse rate increased or decreased proportionately to the height of temperature. Diagnostically significant was a small ulcer, with black crust and erythematous border, most often situated on scrotum, groins or axillae. Local and generalized lymphadenitis, splenic enlargement and a generalized reddish maculopapular rash were usual findings. During the first week, the blood pressure gradually fell to about 90/60, remaining low until desferescence. No evidence of myocardial failure was noted. During the second week slight cyanosis, productive cough and scattered rales were noted in half the number of cases, and depression was marked. Thorough cardiovascular examination, undertaken after patients had been afebrile for at least 30 days, revealed no abnormality. Agglutination of *Proteus vulgaris* OX K was almost invariably positive. Complications included 7 cases of pneumonia, 2 of empyema, symptoms of meningo-encephalitis in 4 patients and partial deafness in one third of the number of cases. The authors discuss the differential diagnosis from malaria, dengue, the enteric fevers and typhus fever. Detailed clinical and necropsy findings in 2 fatal cases are presented. Massive pulmonary atelectasis involving both lower lobes occurred in one. Capillaritis and perivascular infiltration were noted in sections of myocardium, lung, kidney, brain and meninges. The authors conclude that tsutsugamushi fever is an acute infective systemic disease, characterized by pronounced toxæmia and widespread damage to capillaries and arterioles. The clinical picture of hypotension, cyanosis and tachycardia is attributable to peripheral vascular collapse, not to myocardial failure. From their observations, they consider that clinically there is no severe irreversible myocardial damage. The asthenia and tachycardia present during convalescence are not more pronounced than are those which occur after any prolonged severe illness. Constant nursing care, absolute rest in bed and adequate caloric intake are the essential therapeutic measures.

Simulation of mumps—Patterson reports on an unusual case of scrub typhus simulating mumps, which occurred in a soldier aged 34 years. The initial symptoms were a painful swelling of the right side of the face, swelling and redness of the right upper eyelid, frontal

headache and giddiness. On account of the parotid swelling, the patient was admitted to hospital as a case of mumps. His temperature was then 99.4° F. On the second day a small scabbed lesion was noticed at the midpoint of the right upper lid margin. On the fourth day there was a pink macular rash on the trunk, bilateral cervical adenitis, backache and more severe frontal headache. The temperature, which had been remittent in type, rose to 103.4° F. A diagnosis of scrub typhus was made and was confirmed by the Weil-Felix agglutination test. The illness ran a typical course, during which a cough developed as well as inguinal adenitis and a late slight degree of albuminuria. The temperature was normal by the twenty-third day, after which convalescence was uneventful. The eyelid is an unusual site of inoculation in scrub typhus. Its occurrence in this case caused the swelling of the parotid gland which led to the erroneous diagnosis of mumps.

Anderson, C. R. (1944) *J. exp. Med.*, 80, 341.

Berry, M. G., Johnson, A. S., Jun., and Warshauer, S. E. (1945) *War Med.*, 7, 71.

Florio, L., Stewart, Mabel O., and Mugrage, E. R. (1944) *J. exp. Med.*, 80, 165.

Harrell, G. T., Venning, W., and Wolff, W. A. (1944) *J. Amer. med. Ass.*, 126, 929.

Lipman, B. L., Casey, A. V., Byron, R. A., and Evans, E. C. (1944) *War Med.*, 6, 304.

Patterson, H. S. (1944) *Med. J. Aust.*, 6, 138.

UNDULANT FEVER (*Melitensis* and *Suis* Types)

See also B.E.M.P., Vol. XII, p. 361.

Clinical picture

Types

General review.—Staub, in discussing brucellosis (undulant fever), states that it was first classified as a disease affecting dairy herds, the frequency of infection of the human population being overlooked. He estimates that between 10 and 15 per cent of the American population today are infected, the incidence occurring amongst individuals concerned with the handling of cattle or dairy produce. There are three distinct strains of brucella, but Staub is concerned with the disease produced by *Brucella abortus*. Infection can occur either through the alimentary tract or the unbroken skin and a suspect should always be carefully questioned concerning any possible contact with infected cattle. The infection usually, although not invariably, starts with high fever after prodromal fatigue, accompanied by sweating, pallor, muscle and joint pains together with multiple other inconstant symptoms. The attack may last for weeks and relapse into chronicity with periods of remissions. Brucellosis may be misdiagnosed as tuberculosis, pneumonia, malaria and typhoid or other infective fevers. Diagnosis depends upon the results of various laboratory tests: first, blood culture if possible; secondly, an agglutination test, a titre of higher than 1 in 40 suggesting a positive finding; thirdly, repeated opsonocytophagic reactions, which are of value during the course of the illness to show improvement or otherwise; fourthly, leucocyte count and differential counts, since leucopenia with a low polymorphonuclear count is invariably present; fifthly, an intradermal skin test may be of value. The mortality rate is low, but treatment is lengthy, vaccine treatment being the most efficacious when combined with vitamins, iron and liver. Nicotinic acid and thiamin hydrochloride stimulate the production of opsonins and Pentnucleotide is useful against extreme leucopenia.

Staub, R. R. (1944) *Northw. Med.*, Seattle, 43, 274.

UTERUS, DISEASES AND DISORDERS: DISPLACEMENTS

See also B.E.M.P., Vol. XII, p. 426; and Cumulative Supplement, Key Nos. 1581-1584.

Displacements

Retroversion

Uterine suspension.—Gilbert and Aronoff believe that the round ligaments hold the uterus in the position of anteversion and that they also permit it to rotate backwards and forwards at the level of the uterosacral ligaments so as to accommodate the mobile demands made on it by its environment and functions. The authors emphasize the uselessness of suspension operations unless there is also adequate reconstruction of the structures which should support the uterus, bladder and rectum. They describe a stable suspension operation, performed through a Pfannenstiel incision which, however, owing to the risk of infection is contra-indicated for the removal of tumours over 6-8 inches in diameter and for very obese women, in whom the pelvic line may be deep below the already existing virulent infection. The site of incision should not be employed in the presence of normal anatomical relations; it does not election for the Pfannenstiel incision is through the pelvic line. The operation causes minimal trauma to viscera and minimal disturbance of pelvic organs, and it does away with those interfere with the normal mobility and functions of pelvic organs. After the peritoneum has been closed intraperitoneal pockets which may cause obstruction. After the peritoneum has been closed and the recti have been approximated, the round ligaments are sutured to the posterior surface of the aponeurosis with a mattress stitch of nonabsorbable material. Thus the stumps, which after subcutaneous suture may give trouble, are buried.

Gilbert, T. C., and Aronoff, B. L. (1945) *Surg. Gynec. Obstet.*, Internat. Abstr. Surg., 80, 404.

UTERUS, DISEASES AND DISORDERS: PROLAPSE

See also B E M P, Vol XII, p 436

Treatment

Chaffin's operation

A new operation for fourth degree prolapse—Chaffin gives a description of a new operative procedure for vaginal subtotal hysterectomy for the cure of fourth degree prolapse. He reviews other operations designed for the treatment of cystocele which are unsatisfactory because in principle they fail to provide substitutes for the mechanical factors at work, ending usually in amputation of the cervix. The Watkins-Wertheim operation is recommended for cystocele with first or second degree uterine prolapse when the body, anchored to the pubo-vaginal fascia, is interposed between the anterior vaginal wall and the bladder. It is ineffective for fourth or fifth degree prolapse. For these degrees of prolapse, the objectives are to support the bladder, hold up the vaginal vault, preserve the vaginal canal and restore the perineum in order to prevent anal prolapse. The principle of Chaffin's operation is to remove the body and thus make available the round and broad ligaments for support by suturing them to the lower posterior surface of the cervix. In this position they pull the cervix upwards and backwards, thus playing the part of the sacrocervical ligaments. An inverted T incision is made well up to the urethra and the vaginal flap is dissected laterally to the broad ligament. The bladder is dissected upwards and retracted, the peritoneum is opened and the body is pulled out and amputated at the level of the internal os. The clamped ligaments are tied and are sutured firmly into the lower end of the cervix. The amputated end of the cervix is closed and this end, anchored beneath the urethra by suspension sutures through the pubovaginal fascia, acts as effectively as does the fundus in the Watkins-Wertheim operation. The other end is held up by the round and broad ligaments so as to preserve the normal length of the vagina. Restoration of the perineum completes the operation.

Operations

Importance of pre-operative investigation—TeLinde urges careful evaluation of all factors before embarking on surgical treatment of prolapse of the uterus. Each patient presents an individual problem, depending upon her general physical condition, the desirability of preserving menstruation, the desirability of childbearing, the degree of prolapse and the condition of the cervix and the body of the uterus. Anatomical factors must also be considered and in nulliparous women who have done no heavy work congenital weakness of the bases of the broad ligaments must be assumed. The uterus is suspended by the round ligaments, the uterosacral ligaments, the cardinal ligaments and the fasciae, and rests on the muscular floor of the pelvis. Some or all of these structures are utilized in the various operations designed to support the uterus and vaginal tube. In young women desiring more children a pessary should be used if possible and operation deferred because radical plastic vaginal repairs will be injured by subsequent deliveries and the best types of operation are incompatible with pregnancy. Incapacitating prolapse may render operation essential, in such cases the author carries out the necessary vaginal plastic work and some form of intra abdominal round ligament suspension, preferably a modified Gilliam suspension combined with shortening of the uterosacral ligaments and advancement of bladder peritoneum on to the uterus. Recurrence is probable, however, after any type of round ligament shortening. In relatively young parous women desiring no more pregnancies the author treats first degree prolapse by Manchester operation with sterilization. In second and third degree prolapses the Spalding Richardson operation gives satisfactory support and automatically sterilizes. The Watkins operation is contra indicated because by it surgical procedures later in life, for benign or malignant disease, are made difficult. For first degree prolapse in women over 40 years of age the Manchester operation suffices. For good surgical risks of second or third degree the Spalding Richardson operation is indicated but is too long a procedure for patients in poor physical condition, upon these the Watkins transposition operation should be performed if the uterus is healthy and of the proper size. For elderly enfeebled patients with no further sexual interests the Le Fort method of colpocleisis is satisfactory.

Chaffin, R. C. (1944) *Amer J Surg N S*, 68, 328

TeLinde, R. W. (1945) *J Amer med Ass.*, 127, 495

UTERUS, DISEASES AND DISORDERS: TUMOURS

See also B E M P, Vol XII p 448, and Cumulative Supplement, Key Nos 1586-1590

Fibroid tumours

Treatment

Observation, surgery and irradiation—Phaneuf discusses the treatment of myomata of the uterus under three main divisions: observation, surgery and irradiation with radium or deep x-ray. Small symptomless tumours should be kept under observation and the patients should be examined at regular intervals. Larger tumours causing pain and haemorrhage require active treatment. Myomectomy through vagina or abdomen, done in suitable cases in women of childbearing age, makes pregnancy possible with delivery by forceps or Caesarean section. In cases in which myomectomy is not possible hysterectomy becomes necessary, either fundic, supracervical or supravaginal hysterectomy, or panhysterectomy. In supracervical hysterectomy it is essential to ensure that the cervix is healthy and to provide appropriate treatment when there is any doubt. Thorough cauterization of the cervix is the best and simplest method.

Not infrequently carcinoma of the cervix occurs at the same time as, or soon after, supracervical removal of the uterus for fibroids. Myomata of the uterus may also be treated with radium or deep x-ray in suitable cases, care being taken to rule out by a diagnostic curettage the presence of any malignant growth of the endometrium. Improved pre-operative and post-operative care and modern methods have made pelvic operations so safe that hysterectomy may be considered to be the treatment of choice for uterine myomata, the removal of the uterus guarding against a later possible development of carcinoma. In 1,000 consecutive cases of myomata of the uterus which were treated by Phaneuf the youngest patient was 20 and the oldest 76 years of age. In 48 cases complicated by pregnancy 4 patients had tubal pregnancy, and among the total cases the additional pathological lesions found at operation were many and varied. The mortality was 2.8 per cent, and occurred chiefly in the earlier cases before plasma transfusion or sulphonamide drugs had been used. No deaths occurred in the last 386 cases.

Dangers of irradiation.—Barrett argues strongly in favour of the surgical treatment of uterine fibroids and believes that there is but a small number of cases in which irradiation can be considered to be justifiable. He reinforces his views with the results of a questionnaire submitted to leading gynaecologists in various parts of the United States of America and Canada. He points out that irradiation cannot be effective without producing castration and that its use should therefore be restricted to cases of small tumours occurring at the menopause which present no complications and in which the only symptom is slight or moderate bleeding. Surgery, Barrett states, is the only treatment that can diagnose all the conditions or all the complications which may coexist and at the same time remove the whole of the tumour and accompanying tumours and leave all that ought to be left. To treat a large fibroid by irradiation and leave a degenerating tumour for the abdomen to struggle with, making of the abdomen a sarcophagus, neglects possibilities of recurrence or subsequent malignancy which need not be contemplated after adequate surgical interference. Before the menopause, Barrett considers that the use of irradiation is completely unjustifiable; in spite of the relation of fibroids to sterility and abortion, in many cases they still leave the patient with possibilities for childbearing, menstruation and ovarian function. The patient's own oestrogenic laboratories should be preserved; she should not have to fall back on a commercial product. The author maintains that fibroids larger than a 3½ months' pregnant uterus should be removed by hysterectomy at any age, except in cases in which myomectomy is possible during the childbearing age. He does not consider that the large size of a tumour, or its local complications or attachments, or the presence of anaemia or heart and kidney insufficiency, are contra-indications to surgical treatment. Interference with a fibroid complicating pregnancy is not desirable.

Carcinoma

Carcinoma of cervix uteri

Advances in treatment.—Block reviews the present condition of cancer of the cervix in the light of modern knowledge. Early diagnosis is essential, and Schiller's iodine test enables the areas which should be subjected to biopsy to be recognized. Most authorities agree that diagnosis must be made microscopically, and the vaginal smear method has been advocated by Papanicolaou and Traut. Jones and Jones compared the results of panhysterectomy in a selected group of 36 early cervical carcinomata and in 704 unselected cases in all stages treated by irradiation: the 5-year cure rate was respectively 41 and 57 per cent. Complications after radiotherapy are discussed. Aldridge has studied intestinal injuries after irradiation; acute proctosigmoiditis is the mildest form observed, in more severe lesions ulceration usually occurs. Block states that for years irradiation has been advocated by many surgeons as the best method of treatment; recently there has been a tendency in the United States of America to advocate operative treatment in some cases, whereas in Europe there have always been some surgeons who have favoured radical procedure. Bonney in 1936 had done 500 Wertheim operations with an absolute cure rate of 40 per cent; the operative mortality was 14 per cent, mostly due to shock. Meigs believes that surgery should be limited to young and healthy adults with early growths. Pre-operative treatment is important. In a series of 47 early cases there was no operative mortality; it is too early yet to assess the results, but in 8 the lymph nodes were positive. These patients would eventually have died if they had been treated by irradiation; so far only one has died. Taussig in group II cancer of the cervix, in addition to irradiation of the primary tumour has removed the iliac glands; the percentage of 5-year survivals was 15 per cent greater in patients treated thus than in others who did not have lymphadenectomy.

Pelvic lymphadenectomy in the treatment of cervical cancer.—Morton reports on 65 cases of pelvic lymphadenectomy, and discusses the indications in the light of Taussig's theory that recurrence after destruction of the parent cervical cancer by irradiation was in many cases due to relative insensitivity to irradiation of metastatic cancer in the regional lymph nodes; the nodes, he reasoned, should be surgically removed. Morton reviews the literature, correlating the incidence of glandular involvement implies glandular involvement in about half the number of cases and that clinically uninvolved parametria indicate glandular metastases in not more than one-third the number of cases. Of Morton's patients—the average

age of whom was 41.8 years and who were selected because in them the immediate local cervical reaction to radiation was good—61 had the operation completed. Pre-operatively, 35 patients received high voltage irradiation in dosage varying between 2,000 and 4,000 roentgens, to each of 2 anterior and 2 posterior fields, approximately 4,500 milligram hours of radium were distributed in and about the cervix as well. Radium only, in small doses, was used pre-operatively in 28 cases. Lymph node metastases were found in 15 cases, in 11 of which no degeneration was noted. Fibrosis and hyalinization was observed in the nodes of 24 cases which had had pre-operative x-ray therapy and in 10 cases in which only radium had been used. The most significant finding was that the incidence of glandular involvement was 11.4 per cent and 39.3 per cent respectively in the group receiving and in that not receiving pre-operative deep x-ray therapy, notwithstanding that, according to the Schmitz classification, the former group contained many more advanced cases than did the latter group. Morton suggests that if the difference in incidence of glandular involvement can be substantiated by future experience, it is evidence that x-ray therapy can and does destroy cancer in the regional nodes.

Radiotherapy—Sandler discusses the principles of treatment of carcinoma of the neck of the uterus by radiotherapy. Choice of wave length, dosage rate, spacing of treatment and total dosage depend upon the biological response. Since such response varies greatly in individual tumours, generalized methods of applying standard doses are unsatisfactory. Desirable cytological responses include radiation-induced chromosome abnormalities sufficient to cause death of tumour cells of the next generation. Physical disintegration of the parent cell by an unnecessarily large dose of radiation, which damages normal cells and thus hinders the reparative response of the tumour bed, is undesirable. Serial biopsies for the cytological analysis of the radiation effects, which is necessary for the purpose of assessing the biological response and of guiding dosage, should therefore be undertaken in cooperation with a cytologist. Physical problems are connected with definition of the extent of the primary tumour and selection of the total volume of possible secondary invasion. Full cooperation between gynaecologist and radiotherapist is essential. Prior to radium insertion, routine palpation, colposcopy, cystoscopy, proctoscopy and pyelography should ascertain the limits of the primary tumour and the extent of spread, after which the plan of treatment should be decided upon at a joint consultation. Theoretically calculated volume distribution of beams of radiation can be expressed as isodose charts. Variations in uterine and vaginal dimensions, however, and alterations in the relative positions of the pelvic organs during and after treatment, necessitate deviations from theoretically anticipated dispositions of the radium applicators. Analysis of the dose distribution of radium in individual cases may require a physicist's services. After radium has been inserted two plane skiagrams should check the correctness of insertion and should act as records for dose estimation. The radiotherapist must know the volume distribution of radium previously used, so that he can estimate the exact volume of the "radium para-ethal zones"—which comprise the tissues between the radium lethal isodose surface and the pelvic wall, and are often unequal on the two sides of the pelvis—and the irradiation dosage required.

Radium and surgery—Schlink and Chapman describe clinical research into the treatment of cancer of the cervix uteri with radium and by surgery. All patients are given one full dose of radium 5,000 to 7,000 milligram hours, with one millimetre of platinum screenage to the uterus and two millimetres of platinum screenage to the vagina, after 5 weeks cases considered to be operable undergo Wertheim's radical hysterectomy, an operation which the authors state is "a very safe risk" if it is performed, 5 weeks after radium has healed the primary lesion, by an average surgeon in a good hospital environment and with a well trained team. Thus performed the mortality rate of hysterectomy is almost as low as that which attends the use of radium only and the morbidity rate is no greater than that of any major pelvic surgical procedure. By this radical operation the lymphatic glands, which cannot be treated by radiotherapy, are removed. These glands were invaded by microscopically verified cancer in 20 per cent of the authors' operated cases, and their removal may be one explanation of the superiority of the results obtained over those obtained by radiotherapy alone in various other clinics and analysed by Bourne and Williams. Schlink and Chapman suggest that pre-operative radium treatment provides a clean field for operation and explains their low operation mortality rate of 3.5 per cent as compared with a rate of 9–19 per cent in other clinics. The authors' microscopic investigation of thousands of slides of tissue removed at operation has revealed great variability in cancer-cell sensitivity to radiotherapy and has shown that treatment by 5,000 milligram hours of radium produced as many cancer free cervixes as did 7,000 milligram hours.

Carcinoma of corpus uteri

The question of spread to ovary along the uterine tube—Lynch and Dockerty discuss whether or not carcinoma can spread from the uterus to the ovary along the lumen of the uterine tubes, from the practical point of view, also, it has to be determined how much danger lies in curettage of the malignant uterus prior to radium treatment. The authors report on investigations of 113 cases of operable carcinoma of the uterus or ovary or of both, which were observed at the Mayo Clinic. In a group of 51 cases in which the carcinoma had originated in one or both ovaries and had metastasized to the tube but not to the endometrium, no undoubted example of mucosal implantation alone was noted, nor were clumps of carcinoma

cells observed lying free in the tube lumen. Amongst cases of carcinoma of the uterine fundus with involvement of the tube or tubes but without metastasis to the ovaries, there was evidence of submucosal permeation of the lymphatic spaces but none of spread by mucosal implantation alone. A footnote, however, indicates that Dockerty has recently observed two examples of such a mode of spread. In a group of cases of carcinoma of the ovary (or ovaries) and endometrium, with involvement also of the tube or tubes, spread appeared to have been by direct extension or by lymphatic permeation or by both, except in 2 cases in which tubal involvement appeared to be limited to the mucosa. In 11 of 30 cases of carcinoma of the ovary (or ovaries) and endometrium but not of the tubes, the lumen of the tube appeared to have played the part of a passive conduit for the transmission of carcinomatous cells without itself becoming involved.

Diagnosis and differential diagnosis

Periodic pelvic examination: report of a survey.—In a paper on the value of periodic pelvic examination, Macfarlane, Sturgis and Fetterman describe the result of an investigation undertaken by them. By means of appeals to patients, to women's clubs, nurses' auxiliaries, social service agencies and to the public at large through the press, 1,319 volunteers were found, white women between 30 and 80 years of age, married or single, with or without children, from every walk of life. They agreed to submit themselves to examination twice a year for 5 years as a contribution to medical science. Cancerphobia was not produced, on the contrary a sense of security was given. The procedure was simple: a careful bimanual examination and a careful inspection of the cervix in a good light. A total of 9,111 examinations were made and 545 volunteers have completed the 5-year period. Four early cancers of the cervix were found and one early cancer of the uterus; the patients were adequately treated, and remain well, 2 for 6 years, 2 for 5 years and 1 for 15 months after treatment. As well, 461 inflammatory lesions of the cervix were discovered and 200 have been successfully treated. It is concluded that by means of periodic pelvic examinations of presumably well women, (1) early and curable cancer of the cervix uteri can be detected, (2) inflammatory lesions of the cervix, which might predispose to cancer, can be discovered in about 35 per cent of such women and (3) the death rate from uterine cancer could be materially reduced.

General

Prophylactic measures.—Johnstone reviews the prophylaxis of chronic disease and cancer from the obstetrical and gynaecological standpoint. To routine antenatal care is attributable the diminished incidence of eclampsia and severe pregnancy toxæmia—and thus of associated residual arteriorenal damage in survivors—and of urinary infections. Improvement of pregnant women's diet has reduced the incidence of abortions and premature births. Since the widespread use of sulphonamides, mortality from sepsis after childbirth has markedly decreased, with apparently parallel diminished incidence of material disablement caused by the serious sequelae of pelvic infection. More conservative intranatal care has resulted in decreased trauma to the maternal passages. Adequate postnatal care will prevent many minor complaints and much chronic partial invalidism. Johnstone considers also some experimental and statistical findings relating to the cancer problem. Although oestrogenic substances undoubtedly influence the growth of tumours in mice, no clear causal relationship between the sex hormones and cancer development in human beings has been established. Castration in males has retarded the growth of prostatic cancer, and stilboestrol administration has been associated with improvement in some breast cancers. Since breast, cervical and prostatic cancers occur most often after these organs' functional response to the sex hormones has waned, Johnstone speculates whether or not the unutilized hormone has some significance in abnormal growth stimulation. The increased incidence of chronic cervicitis in those who have received less careful intranatal care and less adequate treatment of cervical injuries. Educational propaganda among middle-aged women regarding the early symptoms of cervical cancer would secure earlier diagnosis. A proportion of ovarian and vulvar carcinomata would be prevented if every diagnosed ovarian tumour were removed promptly, and if leucoplakia, so often the precursor of vulval cancer, were treated by excision when medical measures do not speedily cure the early condition.

General Treatment

Vaginal hysterectomy

Statistics of 600 operations.—Emmert describes the technique of operation in 502 private and 98 hospital cases of vaginal hysterectomy, which was worked out by Gellhorn and himself during a period of 14 years. The end results of continued observation for 3 years or longer in the private cases, and for 6 months or longer in the hospital cases, are also described. Out of 600 cases, 524 gave satisfactory results; 76 were unsatisfactory, with 36 cystoceles, 28 rectoceles, 5 enteroceles, 5 incomplete vaginas and 2 urethroceles, that is, 87.33 per cent were successes and 12.66 per cent were failures. The technique and its advantages are described as follows. (1) There is prevention of shock and little loss of blood as well as ease of identification and dissection of the tissues. Local anaesthesia is induced by lateral infiltration of the parametria and the large sympathetic uterine cervical ganglion, and then block of the anterior vaginal wall and posterior vaginal mucosa, with 0.25 per cent Novocain and adrenaline, 3½ drops to the ounce. (2) The anterior cul-de-sac is not opened and the posterior and lateral attachments up to the uterine vessels are cut and ligatured and the posterior and lateral attachments up to

the avascular portion of the broad ligaments are cut (3) The round ligaments are interposed between the bladder and anterior vaginal wall, making it almost impossible for a recurrent cystocele to occur (4) Enterocele is prevented by obliterating the recto uterine pouch and shortening the uterosacral ligaments (5) A moderately deep vagina is assured Ease of accomplishment is claimed for the technique and absence of recurrence of undesirable sequelae The lack of follow-up information and absence of statistics in the literature is deplored

General

Diagnostic methods

Examination of vaginal smears—Jones, Neustaedter and Mackenzie discuss the value of vaginal smears in the diagnosis of early pelvic malignancy Vaginal fluid, obtained by means of a slightly curved glass pipette with an attached rubber suction bulb, inserted high into the vaginal vault, is sprayed over the surface of a microscope slide, spread evenly, fixed, and then stained by Papanicolaou's method In malignant vaginal smears are found (1) large numbers of leucocytes, (2) numerous bacteria, (3) erythrocytes in varying numbers, although these in a few exceptional cases in the very early stages may be absent; (4) a degree of cornification often greater than is seen in non malignant cases, (5) large multinucleated histiocytes, (6) bizarre malignant cells The specific cell in a smear indicative of cervical carcinoma is the aberrant cell, amoeboid, tadpole, saddle bag, or otherwise irregular in outline, containing deeply staining granular cytoplasm and hyperchromatic nucleus which may show mitotic figures The specific cell designating carcinoma of the fundus is the malignant endometrial cell, round or cuboidal and slightly larger than a leucocyte, containing a relatively large granular hyperchromatic nucleus and, frequently, vacuoles which may become large enough to displace the nucleus to the periphery, giving the cell a signet ring appearance The authors describe one case of sarcoma in which the vaginal smear showed no abnormal cells other than spindle cells, and in which leiomyosarcoma of the neck of the uterus was subsequently confirmed From 427 gynecological cases in which the vaginal smear was examined, carcinoma of the neck was diagnosed in 53, carcinoma of the body of the uterus in 37 cases, and sarcoma of the neck in one The vaginal smear diagnosis was confirmed by biopsy or curettage in 82 of the 91 instances False negative diagnoses were made in 7 cases The authors claim that although the test is not infallible, it deserves further use as a preliminary investigation, and that it contributes to earlier diagnosis, and therefore to earlier treatment, of pelvic carcinoma

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VACCINIA AND VACCINATION

See also B E M P, Vol XII, p 515, and Cumulative Supplement, Key No 1595

Vaccination

Operative procedure

The multipressure method—Parish discusses the advantages of the multipressure method of vaccination as practised in America, over the scratch method as adopted in Great Britain The skin, usually over the deltoid muscle, is gently swabbed with acetone, a small drop of lymph is placed on the cleansed area and the "pressures" or punctures are made with the side of the point of a Hagedorn needle A rapid movement of the needle upwards and downwards is made over the area, an eighth of an inch in diameter, with just sufficient force to avoid drawing blood It is claimed that the number of "takes" is just as high, that the method is simple and painless and that reactions are less severe with a minimum of scar formation Only during a smallpox scare or when the lymph is suspect in potency, do the Americans advise vaccination at more than one site The issue of a more reliable lymph is desirable as regards its upper and lower limits of potency A dried lymph would be preferable A lymph potent at the time of its use is of primary importance, unless it is kept on ice, lymph rapidly deteriorates in potency An analysis of the reactions of 214 cases is presented If the individual has no immunity, a typical reaction with some degree of pyrexia occurs With some immunity, conferred by previous vaccination, a moderate reaction occurs A dry dressing should cover the vaccinated site in order to prevent autovaccination at some other part or the accidental vaccination of other people

Parish, H J (1944) *Brit med J*, 2, 781

VEIN DISEASES

See also B E M P, Vol XII, p 526, and Cumulative Supplement, Key No 1596

it is, if necessary, possible to pass it into branches of the vein. Further incisions may be made in the calf and the procedure may be repeated should the pattern of the venous drainage make this necessary. If after 3 days primary thrombosis has not occurred injection of the most prominent veins will almost invariably produce a firm and painless thrombosis in all parts of the vein exposed to diathermy with an almost complete absence of any localized or general reaction, and the patient will be fit for discharge in 5-7 days. Generally speaking, all cases suitable for ligation and retrograde injection are suitable for diathermy and all absolute contra indications apply equally to both methods of treatment.

Trendelenburg's operation

Principles of surgical treatment—Arthur discusses the operative principles underlying successful surgery of varicose veins, citing 3 cases in detail in support of his views. He describes the anatomy of the veins involved and points out that it is necessary to ligate the tributaries of the saphenous vein since ligation of the latter vein alone is not sufficient, even when combined with treatment by injection, to prevent the establishment of collateral circulation and the persistence of a varix above the site of operation. The operation should include four stages: first, dissection, cutting and ligation of the 4 main tributaries of the saphenous veins; secondly the exploration of the main trunk in order to ascertain whether it is single or double; thirdly injection of the vein, and fourthly, at the conclusion of the three previous stages, the removal of a portion of the vein as close as possible to the femoral vein. This procedure should achieve thrombosis and prevent any recurrence. It sometimes may be necessary to ligate the saphenous vein at the knee at the same time if there appears to be much varicosity below the knee, but each case must be assessed on its merits. The patient should always be warned that subsequent injection of a few veins in the calf may be necessary during convalescence. Arthur thinks that Ethamolin (monoethanolamine oleate) is the best solution for injection at the saphenous opening: he employs a fine ureteric catheter, and has not experienced necrosis or deep thrombosis after accidental leakage of the solution into the surrounding tissue.

Phlebitis

Thrombophlebitis

The problems of thrombophlebitis—Jensen discusses the problems presented by thrombophlebitis. He thinks that the term phlebothrombosis, often applied to mild thrombophlebitis, should be reserved to describe the condition of thrombus in injured veins, thus distinguishing it from thrombosis arising, according to Curveiler's theory, from inflammation of the vein wall. The author describes three groups, as follows: (1) The mild or aseptic type occurs spontaneously in either normal or varicose veins. Its aetiology is uncertain but it sometimes results from strenuous activity or firm massage, or it may even have no apparent cause. (2) The moderate type occurs after surgical procedures, the puerperium, systemic infections, notably pneumonia and typhoid fever, and the exanthemata. Although this form displays the characteristics of infection, vein cultures seldom result in growth. (3) In the septic and purulent type bacteria are present in the vein wall and thrombus, which fact explains migration and metastases. Asepsis, early surgery and chemotherapy have lessened the incidence of the third type, notable examples of which are afforded by the purulent lateral sinus thrombosis associated with middle ear disease, cavernous sinus thrombosis appearing after carbuncles, pyelophlebitis and infections of the extremities. Jensen doubts the aetiological significance of allergy. Knowledge of the exact pathology of the condition is incomplete. There are fibrosis of the vein wall and diffuse infiltration of chronic inflammatory cells throughout the vein wall, chiefly around the vasa vasorum. There is inflammation of the contiguous lymphatic vessels with blocking of the main channels. Fluid accumulation in the tissue spaces is increased by local tissue anoxaemia. Clinical manifestations may be absent in the mild or aseptic cases. The author gives detailed reports of 3 cases in 2 of which pulmonary embolism had occurred before the primary condition was clearly recognized. These emboli result, if small, in localized pneumonitis, if large they cause infarcts which may lead to abscess formation, if massive they cause sudden death. Emboli from the portal venous system lead to hepatic infarction and suppuration. Involvement of the cavernous or lateral sinuses, in association with carbuncles or middle ear disease, causes a high rate of mortality. Sequelae are enlarged legs, ulceration and frequent recurrences of thrombophlebitis and much intermittent pain. Prompt ligation is advocated and the potency of the venous system should be determined by phlebography.

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VERTIGO

See also B. E. M. P., Vol. XII, p. 544, and Cumulative Supplement, Key No. 1598

Labyrinthine or aural vertigo

Aural vertigo without suppuration

Ménière's disease—Ménière's disease is discussed by Mogan and Baumgartner, who describe

of phenobarbitone. These doses should be continued as long as symptoms are present. In addition intravenous histamine may be tried, 19 milligrams of histamine acid phosphate being given in 250 cubic centimetres of potassium chloride solution over a period of 1½ hours and repeated daily or less often depending upon the severity of the disease. In 16 cases so treated, 11 patients benefited, 6 of these had had no attacks of vertigo from 1 to 3 years after treatment. Sixteen cases were treated by the Furstenberg diuretic regimen of low sodium diet and administration of ammonium or potassium chloride orally as well as of phenobarbitone. Seven of these patients benefited by the treatment. Histamine is not specific but is a useful therapeutic adjunct. The tinnitus tends to be persistent even after section of the auditory nerve. Surgical treatment should always be delayed for as long a time as is possible.

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VITAMINS

See also B E M P, Vol. XII, p. 570, and Cumulative Supplement, Key Nos. 1601-1609

Water-soluble vitamins

Vitamin B₂ complex and the pellagra preventing (P P') factor

Ariboflavinosis and the eye—Ocular signs of ariboflavinosis are capable of such varying assessment by different observers that the exact incidence of the condition has not so far been accurately determined. Mann states that it is rare in Great Britain and that misinterpretation of normal lumbal loops in a state of congestion has caused some to overrate its frequency. The earliest certain sign of the condition is a budding out of new capillaries from the lumbal loops at their apices with extension on to the true cornea. This should be present in both eyes and around the whole corneal circumference. The final certainty must be the emptying of the new loops after administration of riboflavin. A case is discussed in detail. Both corneae showed marginal vascularization and opacities in the substantia propria. The vascularization was distinctive, being in the form of new parallel radially arranged loops springing from the apices of the loops of the lumbal plexus and extending in arcades beyond this slightly more than half way to the pupil margin. Beyond the tips of the new vessels was a concentric arrangement of opacities. This has not been specially noted before. In the neighbourhood of the opacities vessels were observed passing more deeply into the substantia propria and there was a slit lamp appearance of splitting of the corneal lamellae in the opacities. The blood riboflavin was 17 micromilligrams per 100 millilitres of plasma and dark adaptation was poor in spite of a normal blood vitamin A and carotene content.

Vitamin C and scurvy

Definition of saturation—Zilva states that the minimum requirements of vitamin C are 5 milligrams daily, but an intake of 30 milligrams daily is a reasonable target value. The vitamin has no influence on any condition other than scurvy, and a factor contributing to the prevailing distortion of this view is the application of certain chemical methods of assessment in place of the biological test. The reduction of indophenol is not a specific test for ascorbic acid and the promiscuous use of the method has led to faulty conclusions. Thus the presence of reductone or reductive acid in cooked foodstuffs may seriously interfere with the assessment of vitamin C. The chief reason for the exaggerated views held by many on the requirements of the vitamin for the maintenance of good health is the confusion of thought on the phenomenon termed saturation. One definition of the term demands the daily elimination in the urine of a constant amount of vitamin C after the ingestion of a standard quantity of the vitamin. Arbitrary levels have been adopted by various investigators working with massive doses of ascorbic acid. Many healthy people, however, do not eliminate ascorbic acid in the urine for long periods. In one experiment no signs of scurvy were observed in a subject who was on a scorbutic diet for 100 days. After 9 days the plasma ascorbic acid reached the low value of 0.1 milligram per 100 cubic centimetres. A low level of ascorbic acid in the plasma, therefore, does not necessarily indicate a deficiency of vitamin C.

Vitamin C saturation and its effects—Pijoan and Lozner believe that an assay of the diet is untrustworthy as a method of evaluating ascorbic acid deficiency in any individual. More reliance should be placed on demonstrations that the diet can produce scurvy or a steady linear decline in the vitamin C content of the blood leucocyte platelet layer. One subject was given a diet free from vitamin C until his plasma vitamin value was zero and the blood tissue vitamin value began to decrease steadily. The latter value was subsequently maintained at a constant level after the subject was given small amounts of the vitamin at protracted intervals. There were no scorbutic manifestations at the end of 21 months. At this stage an experimental incision was made in the subscapular region. The wound healed normally, and biopsy showed sufficient formation of collagen and reticulum, with no evidence of weak areas. It appeared that a diet containing from 18 to 25 milligrams of vitamin C daily was sufficient to protect against scurvy and to secure wound healing. Six volunteers were given 500 milligrams of ascorbic acid daily until their tissues were saturated. The amount required to maintain saturation was represented by the excretion in the urine of 80-100 milligrams daily. The subjects were then given a diet lacking in vitamin C but normal in all other respects. The initial saturation was sufficient to ensure a period of protection against scurvy for 5-6 months. After this

time the patients complained of fatigue, lassitude and irritability. Petechial and perifollicular haemorrhages were observed 2 weeks later. Gingivitis failed to appear in 5 cases, a fact which may indicate that the gingival lesion is not scorbutic in origin. It is also concluded that safe dietary allowances lie somewhere between the protective minimum and the saturation level.

Fat-soluble vitamins

Vitamin A

The fate of vitamin A in the small intestine.—Popper and Volk describe an investigation by the method of fluorescent microscopy for the purposes (1) of determining the conditions and the limits of absorption of vitamin A, (2) of comparing the absorption of vitamin A and of fat, and (3) of studying the influence of drugs on the vitamin. The presence of fluorescent vitamin A in the intestinal contents was also investigated. Absorption of vitamin A and of neutral fat in the entire small intestine is apparently similar and takes place via the lymphatic route, vitamin A being carried from the intestinal epithelial cells to the lacteals by neutral fat. Large amounts of vitamin A are destroyed in the intestine but the intestinal bacteria are not responsible for this. In the authors' experiments the protective role of vitamin E or of tocopherol against destruction of vitamin A in the tissues was confirmed but no protective effect in the intestines was apparent. Popper and Volk's observations confirm the hypothesis that saponification of the fats carrying tocopherol and vitamin A separates them; thus vitamin A, deprived of its protective anti-oxidant, is rendered more vulnerable to destruction in the lumen of the intestine until it is taken up by the re-esterified fat in the intestinal villi. Atropine, which has been shown to reduce absorption of vitamin A in man, was proved by the authors' investigations to reduce, in the rat, absorption in the intestinal wall and to increase the vitamin A fluorescence of the intestinal contents, presumably because of its effect on peristalsis. Neostigmine antagonized the atropine effect, increasing the amount of vitamin A in the wall of the intestine and reducing it in the contents. The authors suggest visualization of absorption to be a suitable method of investigating effects of drugs upon absorption of fat-soluble vitamins in the small intestine.

Other vitamins

Vitamin P

Good effects in ocular haemorrhage.—Mathewson describes 2 cases of ocular haemorrhage in which vitamin P was given with satisfactory therapeutic results. The first patient had multiple myeloma and was given x-ray "spray treatment". Bleeding from the nose and bladder started for which no local cause could be found. The patient found that he could no longer see to read and retinal haemorrhages were diagnosed in both eyes. These were most distinct and very extensive in the left eye. Vitamin P was given daily and continued for 6 weeks. No further retinal haemorrhages occurred and the other bleeding stopped. After the vitamin P had been stopped for 20 days the nasal bleeding started again. It ceased after administration of vitamin P had been recommenced. The retinal haemorrhages were absorbed and subsequent ophthalmoscopic examination showed the fundi to be practically normal; the vision remained subnormal. In the second case a woman of 56 years of age had a cataract extraction with capsulotomy and a large peripheral iridectomy. On the third day after operation a hyphaema was seen in the anterior chamber; further bleeding occurred 8 days later when the prognosis for the eye was considered to be poor. Vitamin P was given; there was no further bleeding and the haemorrhage was absorbed satisfactorily. The patient's general condition on discharge from hospital 10 days later appeared to be improved; she looked younger and her skin had lost its previous muddy colour. Mathewson comments that in both these cases after vitamin P had been given no further bleeding took place, the haemorrhages were adequately absorbed and improvement in general health was most noticeable.

Dietetics and applications

Auxiliary treatment by vitamins

Asher considers that the vitamins are of value not only in the prevention and treatment of deficiency diseases but also in the auxiliary treatment of other conditions, as in the case of vitamin C which is often prescribed in the acute fevers. It is in the sphere of auxiliary treatment that the commercial preparations are so useful because larger amounts can be administered than would be possible if natural products were given. If a preparation containing more than one vitamin is used, it is important to ensure that the vitamin for which the product is prescribed is present in sufficient quantity. The daily need of vitamin A amounts to 4,000 units and can be supplied in the form of one capsule of Avoleum or 1 minim of Prepalin. Calciferol is of use when extra vitamin D is necessary to aid in the absorption of calcium. Vitamin D is much less widely distributed in ordinary food than is vitamin A. Therefore it is essential that the preparations should yield the daily requirement of 750 units of vitamin D. Adequate amounts of both vitamins are contained in 4 cubic centimetres of the cod liver oil compound issued by the Ministry of Food. The unit content of this compound is greater than that of most emulsions. The daily dosage of vitamin B₁ amounts to 500 units, but in the case of vitamin B₂ 1,000 units are required. The dosage of nicotinic acid ranges from 30 to 350 milligrams daily. In general, however, the members of the vitamin B complex are widely distributed in ordinary foods so that special preparations are not necessary unless the diet is known to be poor. Infants require 10–30 milligrams of vitamin C daily, but a child or adult should have 50 milligrams daily.

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VULVA AND VAGINA DISEASES

See also B E M P, Vol XII, p 606

Vagina

Vaginitis

Results of treatment in 1,000 cases—Lloyd records the results of investigation and treatment of 1,000 cases of vaginal discharge, nearly half of which were trichomonas infections. This condition affects undoubted virgins and has a predilection for the vagina in pregnancy. Treatment consists of Stovarsol vaginal compound, irrigations with sodium bicarbonate solution and swabbing with half strength Bonney's blue solution. In one case of trichomonas vaginitis all efforts to dislodge the causative organism were without effect. *Monilia vaginitis* deserves wider recognition and will be discovered more often if search is made. In a typical case the vaginal mucosa is covered with the white patches characteristic of *Monilia albicans*. The predominant symptom is a white musty-smelling discharge causing much irritation. The best treatment is the local application of Mersagel fungicidal jelly. The infection is apparently more common during pregnancy. Most cases of senile vaginitis present thin purulent discharge with punctate haemorrhages on the vaginal walls. Satisfactory results can be achieved by giving lactic acid douches and stilboestrol in doses averaging 3 milligrams daily. Non-inflammatory leucorrhoea is characterized by epithelial cells and Doderlein's bacillus but no pus cells on a high vaginal swab. Gonorrhoea is far from being the commonest cause of discharge in women and it may coexist with trichomonas infection. Lloyd recommends treatment with sulphathiazole by the mouth and sulphonamide powder locally. Cases of vulvo-vaginitis of infancy should be admitted to hospital and the patients should be examined under an anaesthetic. Treatment with sulphonamides, instillation of 10 per cent Argyrol and stilboestrol cured all cases in this series after 6 weeks.

Lloyd, O (1945) *Brit med J*, 1, 509

WHOOPIING-COUGH

See also B E M P, Vol XII, p 616, and Cumulative Supplement, Key No 1613

Aetiology

Immunity

Pertussis skin tests in 680 infants—Kunstler analyses the results observed of pertussis skin tests in 680 infants ranging in age from 1 week to 8 months. There is a steady increase in the positive reactions until the child reaches the eighth month, indicating loss of passive immunity with an increasing susceptibility to the disease. An analysis of the figures of pertussis in Montreal in 1937, in which year it was prevalent, shows an increasing incidence in the age groups from 0 to 6 months corresponding to the increasing percentage of positive pertussis skin tests. The curve plotted for pertussis skin tests bears a close relationship to the curve plotted for the Schick test in diphtheria during the same early months of life. In a group of 60 children over 1 year of age, 45 were positive to the pertussis skin test, not having had pertussis, 15 negative to the test, had recently recovered from the disease. Newborn infants, negative to the Schick test for diphtheria, are passively protected by antitoxin which reaches their blood via the placental circulation. In pertussis experimental evidence suggests that an anti endotoxin passes from the mother to the child, the serum of the infant negative to the pertussis skin test neutralizing the pertussis toxin.

Bacteriology and morbid anatomy

Cough plates

Nasal and cough plate cultures compared—Silverthorne, Zacks and Jenkins present the results of examination for the presence of Gram negative bacilli by means of direct smears and cultures of nasal mucus and cough plate cultures. Nasal mucus was obtained by suction applied by a syringe attached to one end of a sterile rubber catheter inserted into the nostril, and the tubing was then returned to a sterile test tube. Culture was made on Bordet medium and incubated for 2-4 days. Cough plates were taken in triplicate and incubated for 2-5 days. Of 54 cases of whooping cough in children of all ages from 7 weeks to 14 years cough plate cultures were positive in 55 per cent, whereas nasal mucus cultures were positive in only 42 per cent of instances. Both culture methods used together were superior to either alone in isolating *Haemophilus pertussis*. The authors conclude that, with their technique, cough plate cultures are superior to nasal mucus cultures in isolating *Haemophilus pertussis*. Direct smears of nasal mucus showed Gram negative bacilli in 44 out of 54 clinical cases of whooping cough, as compared with only 4 out of 33 cases that were not whooping cough. Large numbers of almost exclusively Gram negative bacilli were seen in the direct nasal mucus films from 10 children with clinical whooping cough. The authors suggest that direct nasal mucus smears in the early stage of pertussis may be helpful but not infallible in obtaining

preliminary evidence in the diagnosis of whooping cough, but they hold that a confirmatory culture will be required.

Treatment

Preventive

Alum precipitated pertussis vaccine.—Sako and others present a study undertaken of evaluating in young infants the incidence and severity of reactions after inoculations of alum precipitated pertussis vaccine and of ascertaining their capacity to produce pertussis agglutinins several months after immunization. Sixty-seven per cent of pertussis deaths occur during the first year of life, 47 per cent being recorded as taking place at under 7 months. To lessen this death rate immunization must be carried out in the earlier months of infancy. The study comprises a group of 3,793 infants under 3 months of age, most of them under 2 months, inoculated with 0.2, 0.3 and 0.5 cubic centimetre of the vaccine at monthly intervals. After 6,600 inoculations had been carried out 568 (8.6 per cent) resulted in appreciable reactions of moderate severity with abscess formation in 38 cases. Inoculation is well tolerated by these young infants. In another group of 703 inoculations, 5.5 per cent had appreciable reactions with abscess formation in 23 cases. Systemic reactions accompanied by low or moderate fever occurred in 7.1 per cent of the patients. It does not necessarily follow that a local reaction is always associated with a systemic reaction. Strongly positive agglutination tests, 2–4 months after immunization, were present in 78.2 per cent of 1,834 infants who were observed for some time. In a group of 138 infants 81.2 per cent gave moderate or strongly positive agglutination tests. Tests made 24 months after immunization gave 63 per cent of positive reactions, thus demonstrating the value of immunization in early infancy. The greatest factor in abscess formation is the intracutaneous introduction of some of the alum precipitated vaccine on the point of the needle. To avoid this, a dry sterile needle should be fitted to the previously charged syringe. With this precaution more than 1,000 inoculations have caused no abscess formation.

Diphtheria toxoid for contacts.—Turnbull discusses the clinical use of inoculations of alum precipitated diphtheria toxoid for persons exposed to whooping cough, basing his theories on a series of 61 children, all in close contact with cases of proved pertussis, and in none of whom the disease developed after inoculation. Inoculation of 4 further children failed to avert the attack, so that there was 93.4 per cent protection recorded in the complete series. Inoculations were given just before or at the onset of a non-spasmodic cough and protection was considered to be present if the cough lasted for not more than 10 days after injection. A maximum of 3 subcutaneous injections at weekly intervals was given, children from birth to 3 months receiving 0.5 cubic centimetre toxoid, those from 3 to 12 months 1.0 cubic centimetres and those over 12 months 1.5 cubic centimetres. Turnbull suggests that the persistence of the cough—which in all his cases only vaguely suggested pertussis—for a few days after inoculation denotes an abortive attack of pertussis which should establish lasting immunity. The series showed that optimum results are obtained if inoculations are given during the incubation period and stresses the importance of preventive treatment for the protection of babies, in whom the danger of fatal complications is greatest. It was found that experimental inoculation of rabbits with both alum precipitated diphtheria toxoid and pertussis vaccine gave greater protection than did either antigen alone, and it is believed that the clinical immunity conferred is due to synergy of these two antigens.

Kunstler, Margaret (1945) *Canad. med. Ass. J.*, 52, 62.

Sako, W., Treuting, D. L., Witt, D. B., and Nichamin, S. J. (1945) *J. Amer. med. Ass.*, 127, 379.

Silverthorne, N., Zacks, V., and Jenkins, Effie (1945) *J. Pediat.*, 26, 155.

Turnbull, J. M. (1945) *Amer. J. Dis. Child.*, 69, 5.

YELLOW FEVER

See also B.E.M.P., Vol. XII, p. 660; and Cumulative Supplement, Key No. 1616.

Treatment

Prophylaxis

Relation of infective hepatitis to postinoculation jaundice.—Findlay, Martin and Mitchell¹ record their findings regarding the relation between hepatitis after yellow fever inoculation and infective hepatitis which are based on their observations in 689 cases coming within the former category. It has previously been demonstrated that the icterogenic agent in cases occurring after yellow fever vaccine inoculation was derived from the human serum used as a vehicle in the preparation of the vaccine. Outbreaks of jaundice had been known also to follow the parenteral injection of human blood, plasma, or serum when used for transfusion, or when contained in glycerinated humanized lymph or measles and mumps immune sera. In the cases under review the latent period which preceded the onset of jaundice was longer than it was in infective hepatitis, averaging 101 days. The average time between the onset of symptoms was in infective hepatitis, although sometimes the period was much longer. The condition was usually ushered in by anorexia, nausea, and lassitude, with afterwards in many cases epigastric pain and vomiting. Jaundice and bile in the urine occurred in 432 cases. Except in a small proportion of mild cases liver enlargement was present in all at some stage and the spleen was demonstrable in many. As a rule the degree of pyrexia was low and in most cases it fell within 4 days. Bradycardia usually developed in the second week of jaundice. Tachycardia

was very rare. Rashes, mostly of an urticarial type, were seen occasionally. There were no characteristic blood changes although the leucocyte count not uncommonly showed a neutropenia in the icteric stage. It is now recognized that in epidemics of infective hepatitis cases without manifest jaundice may occur, although the possibility that the same may apply in hepatitis after injection of yellow fever vaccine has received little attention. From observations in postinoculation cases the writers have distinguished three groups: (1) with definite jaundice, (2) with no jaundice but with bile in the urine, and (3) with neither jaundice nor bile in the urine. In this series of cases relapses occurred in about 2 per cent and there was one death. In the fatal case the lesions found were those of subacute hepatic necrosis. In mild cases additional sugar was given by the mouth and in the more severe, intravenous drips were given of 10 per cent glucose-saline with 5-10 units of insulin a day. Clinical and pathological findings did not differ in postinoculation jaundice and infective hepatitis.

In so far as immunology and epidemiology are concerned, Findlay, Martin and Mitchell¹ compare hepatitis after yellow fever inoculation with infective hepatitis. It is mentioned that although there had been no observations of contact spread among cases of postinoculation jaundice the possibility of such contact had been noted by two of the above writers for they had obtained the causal agent from the nasopharynx. It was noted that in areas in which postinoculation hepatitis was rife there was an increase in infective hepatitis, especially when close contact existed. From investigations made into the medical histories of soldiers of all ranks in whom postinoculation hepatitis developed and of those who had been exposed to jaundice infection, it was concluded that the immunity produced by one attack of infective hepatitis was probably considerable. Experimental attempts to transmit the disease to animals, chiefly monkeys, by the sera of patients with postinoculation hepatitis have been inconclusive, but injection of icterogenic serum into a monkey which was on a course of neoarsphenamine caused death with liver necrosis. This did not occur in the case of a control monkey which was given the drug alone. It was known that serum injected into volunteers had produced the disease. Subcutaneous injections of whole blood and of material in solution or suspension from cases of postinoculation hepatitis failed to produce the condition in volunteers, but in 4 cases the passage of yellow fever inoculation jaundice was effected by using the intranasal route and nasal washings from pre-icteric, or very early icteric, patients. The conclusion is reached that the two conditions are due to the same or to very closely allied agents.

Findlay, G. M., Martin, N. H., and Mitchell, J. B. (1944) *Lancet*, 2, 301, 340.
— — — (1944)* *ibid*, 2, 365.

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